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MIAMI UNIV FLA SCHOOL OF MEDICINE  
BIOLOGICAL-MATHEMATICAL MODELING OF CHRONIC TOXICITY. (U)

AFOSR-76-2970

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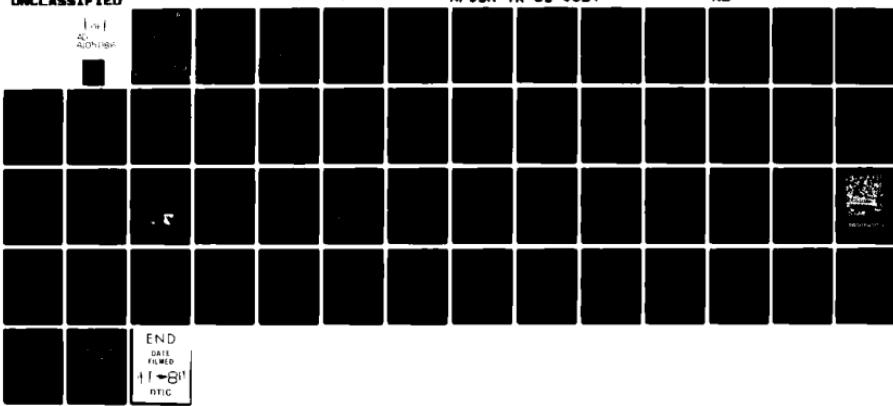
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FINAL SCIENTIFIC REPORT

on

Biological-Mathematical Modeling of Chronic Toxicity

for the period

AFOSR-76-2970-new

February 1, 1978 to May 31, 1981

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| 19 REPORT DOCUMENTATION PAGE   |   |                               | READ INSTRUCTIONS BEFORE COMPLETING FORM |  |
|--|---|-------------------------------|--|--|
| 1. REPORT NUMBER<br>18 AFOSR-TR-81-0624  | 2. GOVT ACCESSION NO.<br>AD-A105086   | 3. RECIPIENT'S CATALOG NUMBER |  |  |
| 4. TITLE (and Subtitle)<br>Biological-Mathematical Modeling of Chronic Toxicity  | 5. TYPE OF REPORT & PERIOD COVERED<br>Final Report 1 Jul 77-31 Dec 78                   |                               |  |  |
| 7. AUTHOR(s)<br>Vera Thomas Ph. D.   | 6. PERFORMING ORGANIZATION REPORT NUMBER<br>M.L. 15 AFOSR-76-2970                       |                               |  |  |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS<br>University of Miami School of Medicine<br>Miami, Florida 33101  | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS<br>61102F<br>2312/A5 15 A57 |                               |  |  |
| 11. CONTROLLING OFFICE NAME AND ADDRESS<br>Air Force Office of Scientific Research<br>Bolling AFB, D.C. 20332  | 12. REPORT DATE<br>22 Jul 81  |                               |  |  |
| 14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)  | 13. NUMBER OF PAGES<br>50   |                               |  |  |
| 15. SECURITY CLASS. (of this report)<br>Unclassified   |   |                               |  |  |
| 15a. DECLASSIFICATION DOWNGRADING SCHEDULE   |   |                               |  |  |
| 16. DISTRIBUTION STATEMENT (of this Report)<br><br>Approved for public release;<br>distribution unlimited.   |   |                               |  |  |
| 17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)   |   |                               |  |  |
| 18. SUPPLEMENTARY NOTES  |   |                               |  |  |
| 19. KEY WORDS (Continue on reverse side if necessary and identify by block number)<br>Pharmacokinetics<br>Mathematical Model<br>Inhalation Toxicology  |   |                               |  |  |
| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br><br>The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination. The main accomplishments of the research are: 1) A general pharmacokinetic model for inhalation administration, based on physiological parameters of the exposed subject and on physical |   |                               |  |  |

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and chemical properties of the inhaled substance, was defined. Mathematical theories and existing programs used in electrical engineering for solution of electric networks were suggested for solution of differential equations ~~for a specific program were~~ prepared. 2) Information on interspecies differences was extracted from the literature; partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat); steady state clearances calculated from pulmonary uptake, and intrinsic clearance determined from vapor distribution in rats were used in the model as elimination rate constants. 3) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: solubility, metabolism, body build, interspecies differences, physical exertion, exposure duration, exposure repetition, and short-term excursion limit. 4) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. 5) Reduced pulmonary uptake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

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## SUMMARY

The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination.

The main accomplishments of the research are: 1) A general pharmacokinetic model for inhalation administration, based on physiological parameters of the exposed subject and on physical and chemical properties of the inhaled substance, was defined. Mathematical theories and existing programs used in electric engineering for solution of electric networks were suggested for solution of differential equations and specific programs were prepared. 2) Information on interspecies differences was extracted from the literature; partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat); steady state clearances calculated from pulmonary uptake, and intrinsic clearance determined from vapor distribution in rat were used in the model as elimination rate constants. 3) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: solubility, metabolism, body build, inter-species differences, physical exertion, exposure duration, exposure repetition, and short-term excursion limit. 4) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. 5) Reduced pulmonary uptake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

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The objectives of the project "Biological-Mathematical Modeling of Chronic Toxicity" were to study the factors affecting the fate of inhaled vapors in the body and to develop a mathematical model to describe their effects on uptake, distribution and elimination. The ultimate goal was to be able to employ the mathematical model to predict optimum exposure conditions for biological testing of chronic toxicity.

In our attempt to explore mathematical modeling in inhalation toxicology, our research took two courses: 1) Development of an animal model to generate information for the simulation model and to corroborate experimentally the predictions made by the simulation model. 2) Development of a general simulation model, based on physiological parameters, for quantitative description of uptake, distribution and elimination of inhaled vapors or gases. The general simulation model was refined in order to make possible studies of various factors which may affect the fate of inhaled vapors in the body. The general simulation model was also simplified in order to accomodate the program on a small programmable pocket calculator. The simplified model uses relatively inexpensive equipment, and the user needs no mathematical skill. The specific simplified programs are designed to be used by practicing toxicologists and hygienists. The program for evaluation of short-term excursion limits is an example.

The main accomplishments of the research are:

1) A general pharmacokinetic model for inhalation administration was defined. This model is based on physiological parameters of the exposed subject and on physical and chemical properties of the inhaled substance. The concept of compartment model was applied.

2) Information on inter-species differences in pulmonary ventilation, tissue perfusion, and body build was extracted from the literature to be available for substituting in the model.

3) Partition coefficients of eight organic solvents were determined for eight tissues of three species (man, monkey, rat). Species differences and effect of meal intake on partition coefficients were under scrutiny.

4) Steady state clearances calculated for man, dog and monkey, from pulmonary uptake rate, were used to define the over-all elimination rate constants in the model.

5) Intrinsic clearances determined from vapor distribution in rat at steady state were used in the model as elimination rate constants of individual elimination pathways.

6) Mathematical theories and existing programs used in electric engineering for solution of electric networks composed from capacitances and conductances are suggested for solution of differential equations describing uptake, distribution and elimination of inhaled vapors.

7) Specific programs were prepared, the most important being for: a) A 10-compartment model in Fortran IV, to be used in large time-shared computer Univac 1100/20. b) A 5-compartment model in basic, to be used on minicomputer Apples II Plus. c) A 2-compartment model to be used in programmable pocket calculator TI-59.

8) The models were used to evaluate the effects of the following parameters on uptake, distribution and elimination of inhaled vapors: a) solubility, b) metabolism, c) body build, d) inter-species differences, e) physical exertion, f) exposure duration, g) exposure repetition, h) short-term excursion limit.

9) Nonlinear dependence of pulmonary uptake on exposure concentration was observed in the animal model. Plateau kinetics, applicable to capacity-limited processes, is suggested for description of elimination processes in the model.

10) Reduced pulmonary uptake and quantitative and qualitative changes in elimination were observed if two vapors were inhaled simultaneously.

Reports and Publications:

(Under Professional name of P.I. - FISEROVA-BERGEROVA)

Methods used in this project and obtained results were reported in detail in interim scientific reports submitted to AFOSR in March of 1979 and 1980, and progress reports submitted in October of 1978, 1979, and 1980. The final interim scientific report follows. Reprints or xerox copies of publications so far resulting from this project are enclosed.

The theories and solutions of the model and supporting data obtained during this project are being prepared for publication in "Modeling of the Uptake Metabolism and Elimination of Some Vapors and Gases", edited by V. Thomas. This monograph will be published by CRC Press in 1982. Manuscripts of four chapters dealing with data and model developed and verified under the AFOSR contract will be submitted to AFOSR in Fall 1981.

Detailed Scientific Report for period: October 1980-May 1981

The main effort was concentrated on finishing the general program for mini-computer Apple II Plus, and on preparing manuscripts for the monograph.

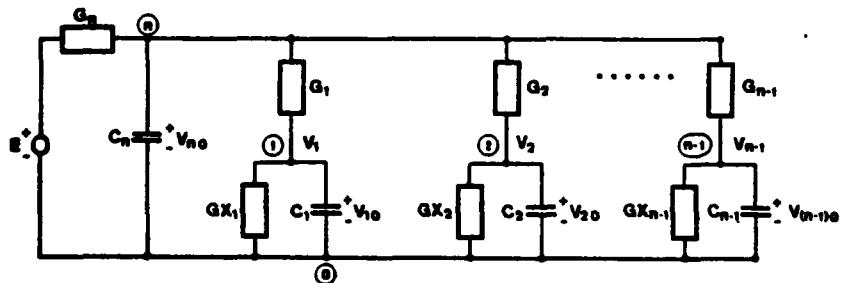
The program solves the general multicompartment model for simulation of inhalation administration. First order kinetics is assumed. The listing of the program is attached.

The general model denoted as LINEAR has the following options:

1) The model can simulate exposure of any subject with defined physiologic parameters to any compound for which partition coefficients and steady state clearance (or intrinsic clearance) are known. From the mathematical point of view, clear-

ance can be located in any tissue or compartment. The compartment can include one or several tissues with similar parameters. The compartments are numbered and the numbers are used as indexes, (*i*), of the elements in the model. The scheme of the general model is in Figure 1. The numbering of the elements (denoted by index *i*) is important. The last elements (*i*=*n*) always relate to respiration. ( $G_{(n)}$ ) = alveolar ventilation;  $C_{(n)} = FRC + 2/3 V_{tid} + \text{lung tissue volume multiplied by lung-air partition coefficient} + \text{volume of arterial blood multiplied by blood-air partition coefficient}$ ;  $V_{(n)} = \text{concentration in alveolar air} = \text{concentration in arterial blood divided by blood-air partition coefficients}$ ). It is convenient to start numbering with those organs or compartments in which elimination takes place, and to assign larger numbers to compartments without clearance. The values of the elements are defined as follows:  $C_{(i)} = \text{tissue (or compartment) volume multiplied by tissue-air partition coefficient}$ .  $G_{(i)} = \text{perfusion multiplied by blood-air partition coefficient}$ .  $G_{x(i)} = \text{clearance multiplied by blood-air partition coefficient}$ . If there is no clearance in the compartment,  $G_{x(i)} = 0$ . All partition coefficients relate to  $37^{\circ}\text{C}$ . Table 1 is designed for convenient preparation of input data (example in table 3).

FIGURE 1

General *n*-Compartment Simulation Model

The element  $G_x$  is removed from those compartments in which no clearance takes place.

TABLE 1

## Preparing Data for LINEAR

| STATEMENT  | READING  |                     |                     |  |
|--|--|---------------------|---------------------|--|
| 50   | No. of compartments, No. of clearances   |                     |                     |  |
| 52-57  | No. compartment: perfusion $x \lambda_{tis/air}$ , volume $x \lambda_{bl/air}$ | $F\lambda_{bl/air}$ | $V\lambda_{bl/air}$ |  |
| 52   | 1: description   |                     |                     |  |
| 53   | 2: description   |                     |                     |  |
| 54   | 3: description   |                     |                     |  |
| 55   | 4: description   |                     |                     |  |
| 58   | $n$ : alveolar ventilation, $V_d$ of lung*                                     |                     |                     |  |
| 60   | Clearance in comp. 1,2,3,4   |                     |                     |  |
| 62   | Printer (indicate in minutes)  |                     |                     |  |
| 64   | How many exposure concentrations?  |                     |                     |  |
| Indicate exposure concentration and duration time in sequence: |  |                     |                     |  |
| 66   | 1: Exposure conc., duration (minutes)  |                     |                     |  |
| 67   | 2: " "   |                     |                     |  |
| 68   | 3: " "   |                     |                     |  |
| 69   | 4: " "   |                     |                     |  |
| 70   | 5: " "   |                     |                     |  |
| "  |  |                     |                     |  |
| "  |  |                     |                     |  |
| 90   | " " "  |                     |                     |  |

$$*V_d = FRC + 2/3 V_{tid} + \text{volume of lung tissue} \times \lambda_{lung/air} + \text{volume of art. blood} \times \lambda_{bl/air}$$

TABLE 2

## Comments to output commands

| STATEMENT | EXPLANATION  | DENOTATION          |                     |
|-----------|--|---------------------|---------------------|
| 1270      | Prints times from the simulation start in minutes<br>(Defined in statement 62).  | TIME =              |                     |
| 1280-1289 | <u>CHOICE: Concentration in tissues divided by tissue-air partition coefficient</u> $[x_{(i)}]$ . Index (i) according to compartment number.   |                     |                     |
| 1280      | Example in listing   | $x_{(1)}$           | $x_{(2)}$           |
| 1281<br>⋮ | add additional compartment if required   | $x_{(3)}$           | $x_{(4)}$           |
| 1290-1299 | <u>CHOICE: Elimination rates</u> $[CUR_{(i)}]$ . Index (i) indicates compartment number except with the last one. The last CUR always indicates the uptake rate or exhalation rate.  |                     |                     |
| 1290      | Example in listing: CUR <sub>(2)</sub> is either uptake rate(+) or exhalation rate (-).  | CUR <sub>(1)</sub>  | CUR <sub>(2)</sub>  |
| ⋮         | add additional clearances if required  |                     |                     |
| 1300-1309 | <u>CHOICE: Total amounts metabolized or excreted</u> $[CYNT_{(i)}]$ . Index indicates compartment number   |                     |                     |
| 1300      | Example in listing   | CYNT <sub>(1)</sub> |                     |
| ⋮         | add additional clearances if required  |                     |                     |
| 1310      | <u>Total pulmonary uptake; Total amount exhaled.</u><br>The indexes do not relate to the model. They change automatically according to number of excretory pathways (defined in statement 50).<br><br>Example in listing: CYNT <sub>(3)</sub> = uptake(+),<br>CYNT <sub>(4)</sub> = exhaled(-) | CYNT <sub>(3)</sub> | CYNT <sub>(4)</sub> |

2) The model accomodates any number of changes in exposure concentration, thus enabling simulation of any kind of exposure. In the input, "number of time section" (statement 64) controls the number of changes in exposure concentrations. Information on exposure concentration and duration of exposure is presented in consecutive order in statements 66-99 (table 1).

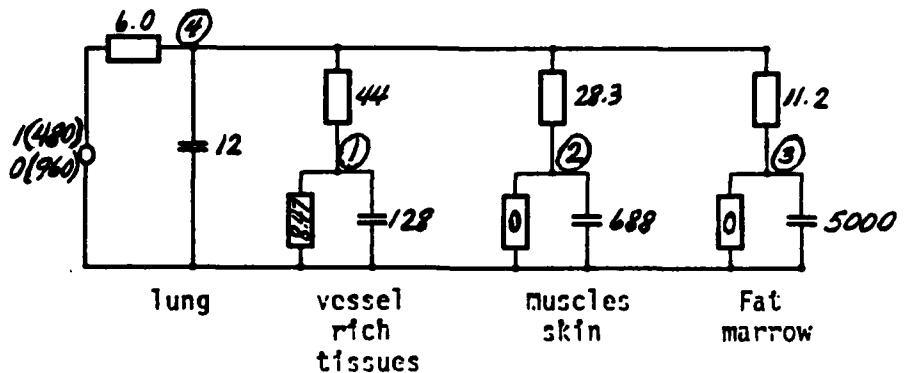
3) The output offers the following information (tables 2 and 4): a) Asymptotic values. Asymptotic values, multiplied by appropriate tissue-air partition coefficient, represent tissue concentrations reached at steady state for exposure concentration equal to 1. b) Time constants and rate constants, which are hybrid constants related to all distribution and elimination processes. These rate constants equal exponent constants in Laplace transform. c) For time intervals, scheduled in minutes (controlled by STEP in statement 62), information is displayed in the following order: First, concentration in all compartments (for  $i = 1$  to  $n$ ), divided by partition coefficients. Second, excretion rates, or metabolic rates, related to clearance  $G_{x(i)}$  (for  $i = 1$  to  $n-1$ ), followed by pulmonary uptake rate (during saturation, positive sign) or exhalation rate (during desaturation, negative sign). Last, the total amounts excreted or metabolized via clearance denoted  $G_{x(i)}$ , followed by total pulmonary uptake and total amount exhaled.

4) The output data is displayed on the screen. On command, the output can also be printed or filed on the disk. The data file is arranged so that it can be used as input in the Appleplot program for graphic display.

Arrangement of input data and output data is shown in a simple example. Four compartment model should be used to simulate eight-hour exposure of a resting man to typical organic solvent (1 mg/l), followed by 16 hour exposure to zero concentration. The data for each eight hours should be printed. The simulation model is pictured in Figure 2. The input data is prepared in table 3 and the printout with commentary is in table 4. The input data is also part of listing of the program (framed statements in listing).

FIGURE 2

## Simulation Model for 8-Hour Exposure to Organic Solvents



Data refers to tables 3-4. Compartment numbers are circled.

TABLE 3

Preparing Data for LINEAR  
Simulation of 8-Hour Exposure to Organic Solvent\*

| STATEMENT | READING  |      |      |     |    |
|-----------|--|------|------|-----|----|
| 50        | No. of compartments, No. of clearances   |      | 4    | 1   |    |
| 52-57     | No. compartment: perfusion $x \lambda_{t1s/air}$ , volume $x \lambda_{b1/air}$ , $F_{b1/air}$ , $V_{b1/air}$ |      |      |     |    |
| 52        | 1: description $4.4 \times 10 ; 6.4 \times 20$   | 44   | 128  |     |    |
| 53        | 2: description $2.83 \times 10 ; 34.4 \times 20$   | 28.3 | 688  |     |    |
| 54        | 3: description $1.12 \times 10 ; 12.5 \times 400$  | 11.2 | 5000 |     |    |
| 55        | 4: description —   | —    | —    |     |    |
| 58        | $n$ : alveolar ventilation, $V_d$ of lung*<br>$n = 4$  |      |      | 6   | 12 |
| 60        | Clearance in comp. ① <sub>2,3,4</sub> $0.847 \times 10$  | 8.47 | 0    | 0   | 0  |
| 62        | Printer (indicate in minutes)  |      |      | 480 |    |
| 64        | How many exposure concentrations?  |      |      | 2   |    |

Indicate exposure concentration and duration time in sequence:

|    |                                       |   |     |
|----|---------------------------------------|---|-----|
| 66 | 1: Exposure conc., duration (minutes) | 1 | 480 |
| 67 | 2: " "                                | 0 | 960 |
| 68 | 3: " "                                |   |     |
| 69 | 4: " "                                |   |     |
| 70 | 5: " "                                |   |     |
| .  |                                       |   |     |
| .  |                                       |   |     |
| 90 | n " "                                 |   |     |

$$*V_d = FRC + 2/3 V_{tid} + \text{volume of lung tissue} \times \lambda_{lung/air} + \text{volume of art. blood} \times \lambda_{b1/air}$$

\*Data are in the listing of program (example).

TABLE 4

Print out for 8-hour exposure to 1 mg/l of an organic solvent.

(Input data in program listing)

ASYMPTOTIC VALUES FOR UNIT EXPOSURE  
CONCENTRATION

|   |  |
|---|--|
| ① | .384 Vessel rich tissue (elimination!) |
| ③ | .45792 muscle, skin                    |
| ③ | .45792 fat, marrow                     |
| ④ | .45792 alveolar air or arterial blood  |

To obtain steady state concentration in tissue (mg/l), the assymptotic values must be multiplied by appropriate tissue-air partition coefficients.

STEP= 480  
# OF TIME SECTIONS= 2  
CONCENTR. mg/l TIME IN MIN  
1 480  
0 960

EXPOENT TIME CONST. minute  
-1.16583694E-03 857.752884  
-.0187986412 53.1953343  
-.246105268 4.06330188  
-7.64555918 .130794881

| SATURATION         |             |  |                               |
|--------------------|-------------|--|-------------------------------|
| concentrations* in | ①           | TIME=480 min after start of simulation | ② .323863796                  |
|                    | ③           |  | ④ .327670372                  |
| metabolic rate     | ①           | 2.32475422                             | ④ 4.03397777 uptake rate      |
| total metabolized  | ①           | 911.673557                             |                               |
| total uptake       | ④           | 2105.08547                             | ④ 0 total exhaled             |
| DESATURATION       |             |  |                               |
| concentrations* in | ①           | TIME=960 min after start of simulation | ② .0574781799                 |
|                    | ③           |  | ④ .0558367587                 |
| metabolic rate     | ①           | .397728989                             | ④ -.335020552 exhalation rate |
| total metabolized  | ①           | 1220.2008                              |                               |
| total uptake       | ④           | 2105.08547                             | ④ -256.65618 total exhaled    |
| TIME=1440          |             |  |                               |
|                    | .0268251847 | .0328285721                            |                               |
|                    | .0665243045 | .0318980546                            |                               |
|                    | .227209315  | -.191388328 exhalation rate            |                               |
|                    | 1366.36937  |  |                               |
|                    | 2105.08547  | -379.78012                             |                               |

\* To obtain concentrations in tissues (mg/l) the values must be multiplied by appropriate tissue-air partition coefficients.

The circled numbers match compartment numbers in Table 3 and Figure 2.

### GENERAL DISCUSSION

Toxic effect is related to the concentration of the substance in the target organ and to the interaction of the substance with receptors. The concentration in the target organ is different from exposure concentration and changes with exposure duration in a predictable way. The interaction with receptors is less predictable. The receptor can be any constituent in the body, usually macromolecules including enzymes which intermediate the metabolism of the inhaled substance. The simulation by our mathematical model predicts quantitatively how the volatile substance gets from the environment to the tissues, but provides no information on interaction with receptor on biotransformation, or on toxic action mechanism.

Modern computer technology and mathematical theories enable solution of multi-compartment models with simultaneous elimination processes. Pharmacokineticists proposed numerous models for dosing and elimination of drugs administered intravenously or orally. Anesthesiologists offered a model for uptake of inert inhalation anesthetics administered at constant alveolar concentration. We proposed the first multicompartment model for simulation of exposure to metabolized (or excreted) vapors and gases (Fiserova-Bergerova, V., Vlach, J., Singhal, K., Simulation and prediction of uptake, distribution, and exhalation of organic solvents, Br.J.Ind.Med., 31, 45, 1974). Since then, we refined the model and searched for experimental designs suitable for obtaining input data for the model. Obtaining input data is nowadays a more difficult task than mathematical solution of the model. The following information and methods were missing, or were inadequate, when we prepared the general simulation model: Methodology for determination of individual elimination rate constants *in vivo* is not fully developed; diffusion constants are known for a very limited number of compounds; information on partition coefficients is scattered; a non-invasive method for determination of cardiac output and its distribution is not commonly available; the significance of extrahepatic metabolism has only recent-

ly been appreciated; no attempt has been made to quantitatively evaluate adsorption and desorption of vapors in respiratory airways. We were able to fill some of these gaps, such as developing animal models for determination of clearance, or obtaining data on clearance and partition coefficients of some substance. But for information on other factors, such as diffusion and perfusion, we relied only on the literature. Some new factors affecting uptake and distribution of inhaled vapors we recognized during the process of model development. Because of lack of time and unavailability of data, we were not able to include these factors in the model. Our observation concerns three particulars:

1) Nonlinear elimination processes. The nonlinear dependence of pulmonary uptake on exposure concentration was observed and was attributed to capacity limited metabolism or excretion. Methods for measuring some parameters describing nonlinearity were developed, and a limited amount of information was obtained in our laboratory and elsewhere (Toxicology Research Laboratory of Dow Chemical Co.; Toxic Hazards Research Unit Department of the Air Force). Mathematical theories suitable for solving the nonlinearity of elimination processes were scrutinized.

2) Additional factors affecting pulmonary gas exchange. We observed that the values of pulmonary uptake rate obtained from the difference between concentrations in ambient air and mixed exhaled air multiplied by minute ventilation were in some instances smaller than the values obtained from the difference between concentrations in ambient air and end exhaled air multiplied by alveolar ventilation. We found three possible explanations: metabolism of vapor in lung tissue; adsorption and desorption of vapors in respiratory airways; and slow diffusion across alveolar membranes. The first possibility is supported by a recently published review of drug metabolism in lungs. (Brandenburger Brown, E.A., The localization, metabolism, and effects of drugs and toxicants in lung, Drug Metabolism Reviews, 3, 33, 1974; Chiou, W.L., Potential pitfalls in the conventional pharmac-

kinetic studies: effects of the initial mixing of drug in blood and the pulmonary first-pass elimination, Journal of Pharmacokinetics and Biopharmaceutics, 7, 527, 1979; Welch, R.M., Cavallito, J., Loh, A., Effect of exposure to cigarette smoke on the metabolism of benzo(a)pyrene and acetophenetidin by lung and intestine of rats, Toxicol. Appl. Pharmacol., 23, 749, 1972). The second possibility is also supported by the literature (Fiserova-Bergerova, V., Teisinger, J., Pulmonary styrene vapor retention, Industrial Medicine and Surgery, 34, 620, 1965; Bardodej, Z., The value and use of exposure tests XII. Mercury exposure test, Ceskoslovenska Hygiena, 8, 157, 1963; Landahl, H.D., Hermann, R.G., Retention of vapors and gases in the human nose and lungs, Archives of Industrial Hygiene and Occupational Medicine, 1, 36, 1950). However, quantitative description of adsorption and desorption in respiratory airways is lacking. We were attempting to fill this gap. The third possibility, the limitation of uptake rate by diffusion, is supported by older literature (Kety, S.S., The theory and applications of the exchange of inert gas at the lungs and tissues, Pharmacological Reviews, 3, 1, 1951; Hunter, A.R., The group pharmacology of anaesthetic agents. I: The adsorption-elimination of inhaled drugs, Brit.J.Anaesth., 28, 244, 1956). However, diffusion is not our priority concern, since there was no systematic deviation of the ratio of concentrations in arterial blood and alveolar air from blood-air partition coefficient.

3) Interference of simultaneously administered xenobiotics. We observed that if two vapors are inhaled simultaneously, the one reduces pulmonary uptake of the other. We expressed the hypothesis that reduced uptake is caused by competitive inhibition of metabolism. Experiments corroborating this hypothesis are underway, but so far no data suitable to application for modeling was obtained.

#### Significance:

With progressing technology, toxicologists and hygienists confront the problem of securing safe exposure to an increasing number of air pollutants. The adverse

biological effect of pollutants, like the therapeutic effect of drugs, is related to blood concentration and/or time integral of concentration in the target organs. Passage of pollutants from the environment to the target organ has the same significance as migration of drugs from site of administration to the target organ. Pharmacokinetics describing the transport of drugs in the body is a potent tool for designing dosage regimens of optimum therapeutic effect. We employed similar methods to propose exposure regimens with equivalent adverse effect. The evaluation is based on comparison of concentrations reached in arterial blood. Two of our observations deserve special attention: 1) The first observation was made while using the program for simulation of short-term increase of exposure concentration. It was calculated that the rising of vapor concentration in tissues depends on the solubility and elimination of the substance. It was demonstrated that if, during the first four hours of an eight hour exposure, the exposure concentration rises for a short period (15 minutes) two or three times, tissue concentrations of well soluble vapors at the end of excursion are smaller than at the end of exposure. Based on this simulation, we suggested to the Threshold Limited Value Airborne Contaminants Committee of American Conference for Industrial Hygienists that short-term excursion limits for industrial pollutants (STEL) should be based on solubility of the vapor, rather than on the average concentration (TWA), as is the current practice. Similar suggestion is made by Japanese investigators (Koizumi, A., Sekiguchi, T., Konno, M., Ikeda, M., Evaluation of the time weighted average of air contaminants with special references to concentration fluctuation and biological half-time, American Industrial Hygiene Association Journal, 41, 693, 1980).

2) The second important observation - the nonlinear dependence of biological effect on exposure concentration - concerns the extrapolation of toxicological data. The observed limited capacity of elimination process can affect the elimination not only quantitatively but also qualitatively. Gehring and Blau discussed mechanism of carcinogenesis with regard to dose dependent changes in metabolic pathways

of inhaled carcinogens (Gehring, P.J., Blau, G.E., Mechanisms of carcinogenesis: dose response, Journal of Environmental Pathology and Toxicology, 1, 163, 1977). We are showing in our experiments with halothane that similar changes in metabolic pathways can be induced if the vapor is inhaled simultaneously with another vapor. The studies show that, in addition to enhancing secondary elimination pathways, the saturation of the major elimination pathways results in the rapid rising of vapor concentration in tissues. The quantitative and qualitative changes introduced by capacity limited processes render dubious the extrapolation of safe exposure concentration from toxicological studies performed at higher exposure concentrations or from studies in which other than inhalation administration was used. In order to prevent an unexpected reaction in the presence of additional xenobiotics (including drugs) exposure concentrations below those which saturate detoxifying mechanisms should be recommended whenever determining the safety limit for occupational or environmental exposure.

It is highly desirable to continue to study the parameters defining nonlinear elimination, and to prepare a general simulation model which accomodates capacity limited processes.

## Program LINEAR (also POMOC)

General Linear model for 5 compartments

JLIST

```

1 REM SEQUENCE OF READING
2 REM N,NGX
3 REM G(I),C(I),I=1...N
4 REM GX(I),I=1...NGX
5 REM (IF NGX=0, NO GX(I) IS READ)
6 REM STEP
7 REM NUMBER OF TIME SECTIONS,NUMSEC
8 REM E(I),TIMEND(I),I=1...NUMSEC

50 DATA 4.1
52 DATA 44.128
53 DATA 28.3.688
54 DATA 11.2.5000
58 DATA 6.12
60 DATA 8.47
62 DATA 480
64 DATA 2
66 DATA 1.480
68 DATA 0.960
100 DIM A(6,6),B(6,6,7),C(6),CC(7)
110 DIM G(6),GX(6),XT(6),XYNT(6),CUR(6)
120 DIM CYNT(8),TD(30),MSTE(30),E(30)
130 DIM X(6),RR(6),XM(6)
135 DIM W(6)
140 DIM BB(7),H(7),D(11),Z(200)
150 DIM TS(100),NAP(100,6)
160 DIM PROUD(100,6),WZ(100,8)
170 READ N,NGX
180 PRINT "N=",N
181 PRINT "NGX=",NGX
190 N1 = N + 1
200 N2 = N - 1
210 N5 = NGX + 1
220 N6 = NGX + 2
230 N7 = NGX + 3
231 NM1 = N - 1
240 REM INITIALIZATION
250 FOR I = 1 TO N
260 XM(I) = 0
270 XYNT(I) = 0
280 X(I) = 0
285 W(I) = 0
290 GX(I) = 0
300 NEXT I
305 PRINT

```

TABLE 1

```
310 REM READ ELEMENTS
311 PRINT "G(I)          C(I)"
320 FOR I = 1 TO N
330 READ G(I),C(I)
340 PRINT G(I),C(I)
350 NEXT
360 IF NGX = 0 GOTO 420
361 PRINT
362 PRINT "NGX(I)"
370 FOR I = 1 TO NGX
380 READ GX(I)
390 PRINT I,GX(I)
400 NEXT I
402 REM START PRINTER
404 INPUT "WANT PRINTER? (Y/N)":RS
406 IF RS = "Y" THEN PR# 1
410 REM CALCULATE ASYMPTOTS
420 GOSUB 5000
425 W(N) = G(N)
426 PRINT
430 GOSUB 5500
431 PRINT "ASYMPTOTIC VALUES FOR UNIT
432 PRINT "          CONCENTRATION"
440 FOR I = 1 TO N
450 PRINT I,X(I)
460 NEXT I
470 FOR I = 1 TO N
480 X(I) = 0
490 W(I) = 0
510 NEXT I
510 PRINT
515 REM SIMULATION INFORMATION
520 READ SEP
530 PRINT "STEP=",SEP
540 READ NUS
550 PRINT "# OF TIME SECTIONS=",NUS
554 PRINT
555 PRINT "CONCENTR.          TIME IN MIN"
560 FOR I = 1 TO NUS
570 READ E(I),TD(I)
580 PRINT E(I),TD(I)
590 NEXT I
700 FAN = G(N) / C(N)
710 GOSUB 3000
720 GOSUB 3160
730 GOSUB 3890
740 T = 0
750 IT = 0
760 UOLD = 0
770 FZ = 0
780 FOR I = 1 TO NUS
790 MSTE(I) = TD(I) / SEP
800 NEXT I
810 PRINT
```

```
820 REM START OF SIMULATION
830 FOR JJ = 1 TO NUS
840 MM = MSTE(JJ)
850 FOT = E(JJ)
860 FOR JK = 1 TO MM
870 FZ = FZ + FOT * SEP
880 T = T + SEP
890 IT = IT + 1
900 TS(IT) = T
910 REM CALCULATE X(I),XYNT(I) - CONCENTRATIONS
920 FOR L = 1 TO N
930 S1 = 0
940 S2 = 0
950 FOR M = 1 TO N
960 S1 = S1 + A(L,M) * XM(M)
970 S2 = S2 + B(L,M,N1) * XM(M)
980 NEXT M
990 XT(L) = S1 + C(L) * FOT
1000 U = S2 + CC(L) * FOT
1010 XYNT(L) = U + XM(L)
1020 NEXT L
1030 REM TRANSFER X(I),XYNT(I)
1040 FOR L = 1 TO N
1050 XM(L) = XYNT(L)
1060 X(L) = XT(L)
1070 NAP(IT,L) = X(L)
1080 NEXT L
1090 REM CALCULATE CUR(I),CYNT(I) - RATES AND AMOUNTS
1100 IF NGX = 0 THEN GOTO 1170
1110 FOR I = 1 TO NGX
1120 CUR(I) = GX(I) * X(I)
1130 PROUD(IT,I) = CUR(I)
1140 CYNT(I) = GX(I) * XYNT(I)
1150 WZ(IT,I) = CYNT(I)
1160 NEXT I
1170 CUR(N5) = G(N) * (FOT - X(N))
1180 PROUD(IT,N5) = CUR(N5)
1190 CYNT(N5) = G(N) * (FZ - XYNT(N))
1200 WZ(IT,N5) = CYNT(N5)
1210 U = CYNT(N5) - UOLD
1220 IF U > 0 THEN CYNT(N6) = CYNT(N5) + U
1230 IF U < 0 THEN CYNT(N7) = CYNT(N7) + U
1240 UOLD = CYNT(N5)
1250 WZ(IT,N6) = CYNT(N6)
1260 WZ(IT,N7) = CYNT(N7)
1265 REM DISPLAY DATA (SEE OUTPUT TABLE)
1269 PRINT
1270 PRINT "TIME="T
1280 PRINT X(1),X(2)
1281 PRINT X(3),X(4)
1290 PRINT CUR(1),CUR(2)
1300 PRINT CYNT(1)
1310 PRINT CYNT(3),CYNT(4)
1320 NEXT JK
1330 NEXT JJ
```

TABLE 2

```
1335 REM FILE DATA
1339 PRINT
1340 INPUT "WANT FILE? (Y/N)":RS
1345 IF RS = "N" THEN END
1350 F$ = "RESULT"
1360 D$ = CHR$(4)
1370 PRINT D$;"OPEN";F$
1380 PRINT D$;"DELETE";F$
1390 PRINT D$;"OPEN";F$
1400 PRINT D$;"WRITE";F$
1410 PRINT N
1420 PRINT N5
1430 PRINT N7
1440 PRINT IT
1450 FOR I = 1 TO IT
1460 PRINT TS(I)
1470 FOR J = 1 TO N
1480 PRINT NAP(I,J)
1490 NEXT J
1500 FOR J = 1 TO N5
1510 PRINT PROUD(I,J)
1520 NEXT J
1530 FOR J = 1 TO N7
1540 PRINT WZ(I,J)
1550 NEXT J
1560 NEXT I
1570 PRINT D$;"CLOSE";F$
1575 REM ORGANISE DATA
1590 Z(0) = IT
1600 Z(1) = 0
1610 FOR JM = 1 TO 3
1620 IF JM = 1 THEN NK = N
1630 IF JM = 2 THEN NK = N5
1640 IF JM = 3 THEN NK = N7
1650 FOR J = 1 TO NK
1660 IF JM = 1 THEN GOSUB 4670
1670 IF JM = 2 THEN GOSUB 4740
1680 IF JM = 3 THEN GOSUB 4810
1690 FOR I = 1 TO IT
1700 MM = 2 * I
1710 Z(MM) = TS(I)
1720 MM = MM + 1
1730 IF JM = 1 THEN Z(MM) = NAP(I,J)
1740 IF JM = 2 THEN Z(MM) = PROUD(I,J)
1750 IF JM = 3 THEN Z(MM) = WZ(I,J)
1760 NEXT I
1770 GOSUB 4560
1780 NEXT J
1790 NEXT JM
1800 END
```

```
3000 REM FORMULATION OF THE SYSTEM MATRIX
3010 FOR I = 1 TO N
3020 FOR J = 1 TO N
3030 A(I,J) = 0
3040 NEXT J
3050 NEXT I
3060 N2 = N - 1
3070 S1 = 0
3080 FOR I = 1 TO N2
3090 A(I,I) = - (G(I) + GX(I)) / C(I)
3100 A(N,I) = G(I) / C(N)
3110 A(I,N) = G(I) / C(I)
3120 S1 = S1 + G(I)
3130 NEXT I
3140 A(N,N) = - (S1 + G(N)) / C(N)
3150 RETURN
3160 REM SUBROUTINE LEVER
3170 FOR K = 1 TO N1
3180 FOR I = 1 TO N
3190 FOR J = 1 TO N
3200 B(I,J,K) = 0
3210 NEXT J
3220 NEXT I
3230 NEXT K
3240 FOR I = 1 TO N
3250 B(I,I,1) = 1
3260 NEXT I
3270 L = 2
3280 LM = L - 1
3290 FOR I = 1 TO N
3300 FOR J = 1 TO N
3310 S1 = B(I,J,L)
3320 FOR K = 1 TO N
3330 S1 = S1 + A(I,K) * B(K,J,LM)
3340 NEXT K
3350 B(I,J,L) = S1
3360 NEXT J
3370 NEXT I
3380 REM CALCULATE TRACE
3390 S1 = 0
3400 FOR I = 1 TO N
3410 S1 = S1 + B(I,I,L)
3420 NEXT I
3430 C(LM) = - S1 / LM
3440 FOR I = 1 TO N
3450 B(I,I,L) = B(I,I,L) + C(LM)
3460 NEXT I
3470 IF L > N GOTO 3500
3480 L = L + 1
3490 GOTO 3280
3500 FOR I = 1 TO N
3510 CC(I + 1) = C(I)
3520 NEXT I
3530 CC(1) = 1
```

```
2540 REM CALCULATE THE EXPONENTS
2550 EPS = 1E - 16
2560 LIM = 100
2570 GOSUB 4120
2580 REM CALCULATE THE RESIDUES
2590 FOR L = 1 TO N
2600 RL = RR(L)
2610 PROD = 1
2620 FOR K = 1 TO N
2630 IF L = K GOTO 3650
2640 PROD = PROD * (RL - RR(K))
2650 NEXT K
2660 C(L) = PROD
2670 NEXT L
2680 FOR I = 1 TO N
2690 FOR J = 1 TO N
2700 FOR K = 1 TO N
2710 CC(K) = B(I,J,K)
2720 NEXT K
2730 FOR L = 1 TO N
2740 RL = RR(L)
2750 PVA = CC(1)
2760 FOR K = 2 TO N
2770 PVA = PVA * RL + CC(K)
2780 NEXT K
2790 B(I,J,L) = PVA * C(L)
2800 NEXT L
2810 NEXT J
2820 NEXT I
2825 PRINT
2826 PRINT "EXPONENT" TIME CONST.
2830 FOR L = 1 TO N
2835 U = - 1 / RR(L)
2840 PRINT RR(L),U
2850 FOR I = 1 TO N
2860 NEXT I
2870 NEXT L
2880 RETURN
2890 REM CALCULATE EXPONENTIALS AND INTEGRALS
2900 FOR I = 1 TO N
2910 CC(I) = 0
2920 C(I) = 0
2930 FOR J = 1 TO N
2940 A(I,J) = 0
2950 B(I,J,N1) = 0
2960 NEXT J
2970 NEXT I
2980 FOR K = 1 TO N
2990 EU = EXP (RR(K) * SEP)
3000 EU = (EU - 1) / RR(K)
3010 EW = (EU - SEP) / RR(K)
3020 FOR I = 1 TO N
3030 C(I) = C(I) + B(I,N,K) * EU + FAN
3040 CC(I) = CC(I) + B(I,N,K) * EW + FAN
3050 FOR J = 1 TO N
3060 A(I,J) = A(I,J) + B(I,J,K) * EU
3070 B(I,J,N1) = B(I,J,N1) + B(I,J,K) * EU
3080 NEXT J
3090 NEXT I
3100 NEXT K
3110 RETURN
```

```
4120 REM ROOT-FINDING STEERING ROUTINE
4130 FOR I = 1 TO N1
4140 BB(I) = CC(I)
4150 NEXT I
4160 XX = 0
4170 NO = N
4180 NP = N1
4190 FOR IROOT = 1 TO N
4200 ITER = 0
4210 GOSUB 4420
4220 ITER = ITER + 1
4230 IF ITER < LIM GOTO 4260
4240 PRINT "ITERATIONS EXCEEDED"
4250 END
4260 DX = - FU / DN
4270 XX = XX + DX
4280 U = ABS (DX)
4290 IF U > EPS THEN GOTO 4210
4300 RR(IROOT) = XX
4310 GOSUB 4360
4320 NO = NO - 1
4330 NP = NP - 1
4340 NEXT IROOT
4350 RETURN
4360 REM DEFLATION OF THE POLYNOMIAL
4370 IF NP < 2 THEN GOTO 4410
4380 FOR K = 2 TO NP
4390 BB(K) = BB(K) + BB(K - 1) * XX
4400 NEXT K
4410 RETURN
4420 REM POLYNOMIAL EVALUATION
4430 FOR I = 1 TO NP
4440 H(I) = BB(I)
4450 NEXT I
4460 FOR I = 2 TO NP
4470 H(I) = H(I) + XX * H(I - 1)
4480 NEXT I
4490 FU = H(NP)
4500 IF NO = 1 THEN GOTO 4540
4510 FOR I = 2 TO NO
4520 H(I) = H(I) + XX * H(I - 1)
4530 NEXT I
4540 DN = H(NO)
4550 RETURN
```

```
4555 REM FILE ORGANISED DATA
4560 D$ = CHR$(74)
4570 PRINT D$;"OPEN";F$
4580 PRINT D$;"DELETE";F$
4590 PRINT D$;"OPEN";F$
4600 PRINT D$;"WRITE";F$
4610 ML = 2 * IT + 1
4620 FOR I = 0 TO ML
4630 PRINT Z(I)
4640 NEXT I
4650 PRINT D$;"CLOSE";F$
4660 RETURN
4670 IF J = 1 THEN F$ = "NAP1"
4680 IF J = 2 THEN F$ = "NAP2"
4690 IF J = 3 THEN F$ = "NAP3"
4700 IF J = 4 THEN F$ = "NAP4"
4710 IF J = 5 THEN F$ = "NAP5"
4720 IF J = 6 THEN F$ = "NAP6"
4730 RETURN
4740 IF J = 1 THEN F$ = "PROUD1"
4750 IF J = 2 THEN F$ = "PROUD2"
4760 IF J = 3 THEN F$ = "PROUD3"
4770 IF J = 4 THEN F$ = "PROUD4"
4780 IF J = 5 THEN F$ = "PROUD5"
4790 IF J = 6 THEN F$ = "PROUD6"
4800 RETURN
4810 IF J = 1 THEN F$ = "INGR1"
4820 IF J = 2 THEN F$ = "INGR2"
4830 IF J = 3 THEN F$ = "INGR3"
4840 IF J = 4 THEN F$ = "INGR4"
4850 IF J = 5 THEN F$ = "INGR5"
4860 IF J = 6 THEN F$ = "INGR6"
4870 IF J = 7 THEN F$ = "INGR7"
4880 IF J = 8 THEN F$ = "INGR8"
4890 RETURN
5000 REM LU FACTORIZATION
5010 D(N) = 0
5020 FOR I = 1 TO NM1
5030 D(I) = G(I) + GX(I)
5040 L = N + I
5050 D(L) = - G(I) / D(I)
5060 D(N) = D(N) + G(I) * (1 + D(L))
5070 NEXT I
5080 D(N) = D(N) + G(N)
5090 RETURN
5500 REM SUBROUTINE LUSOL
5520 Z(N) = W(N)
5530 FOR I = 1 TO NM1
5535 Z(N) = Z(N) + Z(I) * G(I)
5540 Z(I) = W(I) / D(I)
5550 NEXT I
5560 Z(N) = Z(N) / D(N)
5570 U = Z(N)
5580 FOR I = 1 TO NM1
5590 L = N + I
5600 X(I) = Z(I) - D(L) * U
5610 NEXT I
5620 W(N) = U
5630 RETURN
```

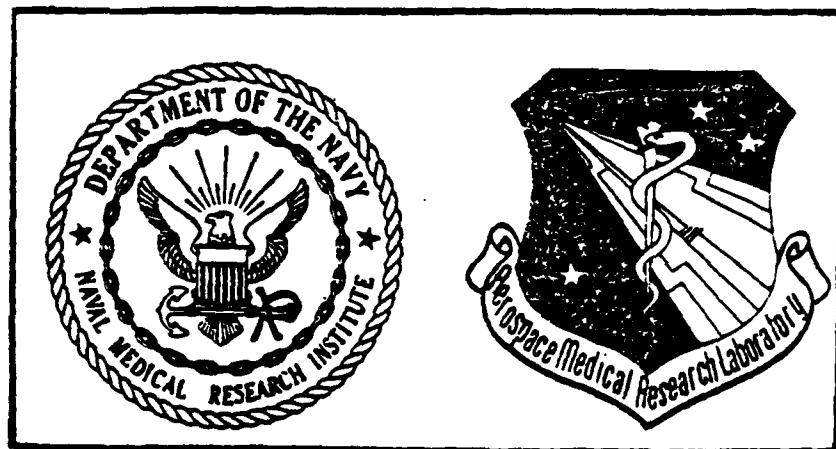
AFAMRL-TR-79-121

**PROCEEDINGS OF THE TENTH CONFERENCE  
ON ENVIRONMENTAL TOXICOLOGY  
13, 14, AND 15 NOVEMBER 1979**

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APRIL 1980

Approved for public release; distribution unlimited.



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## DETERMINATION OF KINETIC CONSTANTS FROM PULMONARY UPTAKE

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The adverse biological effect of an air pollutant is related to its concentration and/or time integral of concentration in the target organ. The passage of pollutant from the environment to the target organ is a dynamic process, determined by the physical and chemical properties of the pollutant and by the physiological parameters of the exposed subject (Eger, 1963). Inhaled, nonwater soluble vapors are removed from the body by pulmonary and metabolic clearance. Since pulmonary clearance takes place only after the end of exposure (or when exposure concentration decreases), the vapor is removed during exposure only by metabolic clearance (Fiserova-Bergerova et al., 1974).

Metabolic clearance in vivo is usually defined by the half-time of disappearance of the xenobiotic from plasma after bolus administration, or as the half-time of urinary excretion of xenobiotic metabolites. The determination of plasma clearance requires frequent blood sampling, which imposes stress on subjects. The urinary excretion of metabolites is affected by a variety of factors, such as distribution of metabolites in the body, binding, and renal clearance.

Inhalation administration makes possible a noninvasive, accurate measurement of the rate of overall metabolism of inhaled vapors (Teisinger and Soucek, 1952).

The pulmonary uptake rate,  $\dot{u}$ , is the sum of retention rates of vapor in tissues,  $\dot{u}_{tis}$ , and the rate of overall metabolism,  $\dot{u}_m$ :

$$\dot{u} = \dot{u}_{tis} + \dot{u}_m \quad (1)$$

The pulmonary uptake can be determined from the difference between vapor concentrations in inhaled and mixed-exhaled air multiplied by minute ventilation:

$$\dot{u} = (C_{inh} - C_{exh}) \dot{V} \quad (2)$$

where  $C_{inh}$  and  $C_{exh}$  are vapor concentrations (mg/liter) in inhaled air and in mixed-exhaled air, and  $V$  is minute ventilation (liter/minute).

We have presented a compartmental model which can be used to determine the retention rate of inhaled vapor in tissues. Using three compartments (VRG - vessel rich tissues, MG - muscles and skin, FG - fat and fat marrow), the retention rate:

$$\dot{u}_{tis} = C_{alv} \left[ F_{VRG} \lambda_{bl/air} \exp \left( - \frac{F_{VRG}}{V_{VRG} \lambda_{VRG/bl}} t \right) + F_{MG} \lambda_{bl/air} \exp \left( - \frac{F_{MG}}{V_{MG} \lambda_{MG/bl}} t \right) + F_{FG} \lambda_{bl/air} \exp \left( - \frac{F_{FG}}{V_{FG} \lambda_{FG/bl}} t \right) \right] \quad (3)$$

where  $F$ 's are blood flows (liter/minute) through the compartments,  $V$ 's (l) are their volume.  $\lambda$ 's are the corresponding partition coefficients of inhaled vapor at 37°C,  $C_{alv}$  is the vapor concentration (mg/liter) in alveolar air, and  $\exp$  is the natural logarithm.

Substituting from Equations 2 and 3 in Equation 1, the rate of overall metabolism can be determined. Since the retention of vapor in tissues is an exponential function, the retention rate diminishes with exposure duration. This determination is most accurate during apparent steady state, when retention by tissues is small ( $\dot{u}_m \gg \dot{u}_{tis}$ ).

We demonstrated the effect of metabolism on pulmonary uptake in an informed volunteer patient who was anesthetized with fluroxene ( $CH_2:CH.O.CH_2.CF_3$ ) in the presence of a small concentration of non-metabolized isoflurane ( $CHF_2$ ). $CHCl.CF_3$ ) (Fiserova-Bergerova and Holaday, 1979). The amount of metabolites accounts for less than 1% of isoflurane uptake (Holaday et al., 1975), and about 45% of fluroxene uptake (Gion et al., 1974).

During anesthesia, samples of inhaled gas and end-exhaled gas were drawn during the appropriate phase of respiration via a nylon cannula inserted in the endotracheal tube at 4 to 10 minute intervals. Mixed-exhaled gas was obtained at the same time at the outlet of a mixing chamber interposed in the expiratory breathing tube. Gas samples were collected in 20 ml glass syringes. At the same time,

minute ventilation was measured with a Wright respirometer. The cumulative uptake D was determined: (1) from the amount of anesthetics delivered by syringe in the closed anesthetic circuit, and (2) from the sum of the differences between concentrations of inhaled and mixed-exhaled air multiplied by minute ventilation, and time intervals between sampling (t in minutes)

$$D = \sum V_t (C_{inh} - C_{exh}) \quad (4)$$

The cumulative uptake predicted by integration of Equation 3 as retention in tissues correlates with the measured uptake of isoflurane (calculated by Equation 4), but the measured fluroxene uptake greatly exceeds the calculated fluroxene retention in tissues (Figure 1). The difference accounts for fluroxene metabolism.

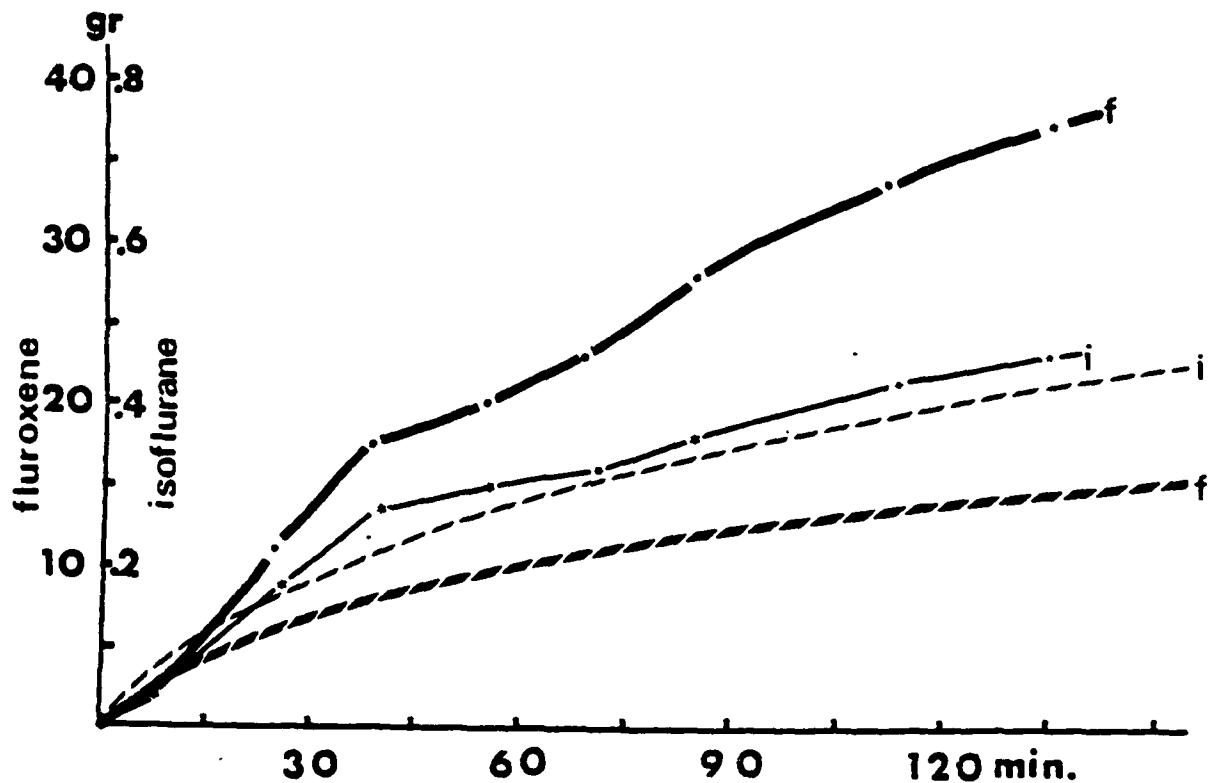


Figure 1. Cumulative uptake of isoflurane (i) and fluroxene (f) administered simultaneously to a surgical patient. Cumulative uptake is plotted against the time after the start of anesthesia. The dashed lines are uptake curves predicted by integration of Equation 3 for alveolar concentrations of fluroxene (154 mg/liter) and isoflurane (3 mg/liter).

To study the effect of exposure concentration on pulmonary uptake, the following assumptions were made: (1) the retention of vapor in tissue is a first order process, which means its rate constant is concentration independent; and (2) metabolic clearance is a limited-capacity process described by Michaelis-Menten kinetics.

To determine the Michaelis-Menten constants in vivo, we exposed male rhesus monkeys (approximately 3 kg) consecutively to three concentrations of one of the following compounds: benzene, halothane ( $CF_3CHClBr$ ), methylene chloride, or trichloroethylene. Concentrations were in the range of TLV during the first exposure; equal to five times TLV during the second exposure; and equal to 25 TLV during the third exposure. In order to reach apparent steady state, each exposure lasted approximately two and one-half hours. Vapors were administered in light sernylan anesthesia via endotracheal tube. The following parameters were measured: (1) vapor concentrations in inhaled air ( $C_{exp}$ ), mixed-exhaled air ( $C_{exh}$ ), and end-exhaled ( $C_{alv}$ ) and arterial blood ( $C_{art}$ ); (2) blood-gas partition coefficients ( $\lambda_{bl/air}$ ); (3) minute ventilation; (4) blood pressure and pulse rate; and (5) blood gases and  $PCO_2$  in mixed-exhaled air. Uptake rate, metabolic rate, and alveolar ventilation were calculated from the measured data. Apparent Michaelis-Menten constants of overall metabolism in vivo ( $K_m$ ) were calculated from double reciprocal plots of metabolic rate versus  $C_{alv}$ ,  $C_{exp}$ , or  $C_{art}/\lambda_{bl/air}$  (measured at a steady state), and versus calculated concentrations in tissues.

In Figure 2, the double reciprocal plots from benzene and methylene chloride are presented.  $K_m$  values related to the concentrations in alveolar air at steady state for all four studied compounds are in Table 1.

Figures 3 and 4 demonstrate double reciprocal plots of metabolic rates of trichloroethylene and halothane versus exposure concentration, alveolar concentration, arterial concentration, and tissue concentration. The data indicate that  $K_m$  values depend on the site in which the concentration is measured, but the maximum metabolic rate ( $V_{max}$ ) is the same regardless of whether it is derived from concentration in inhaled air, alveolar air, arterial blood, or tissue.

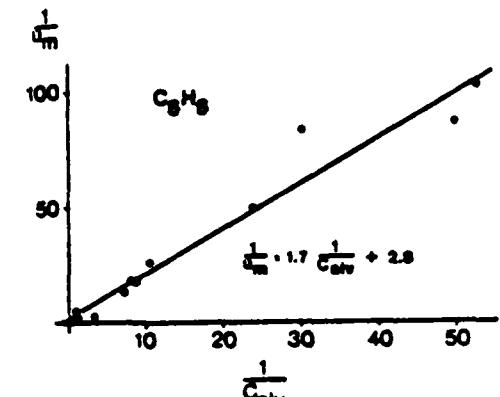


Figure 2. Double reciprocal plot of uptake rates of benzene and methylene chloride versus alveolar concentration. The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

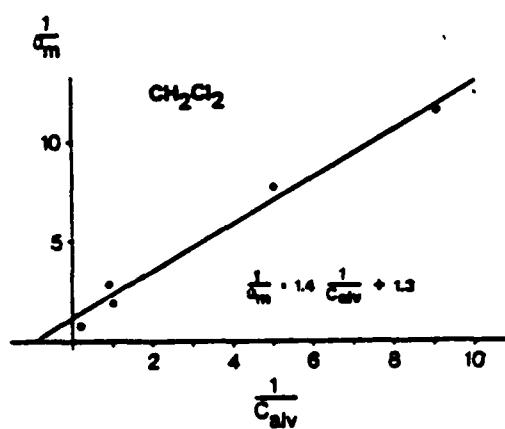


TABLE 1. APPARENT MICHAELIS-MENTEN CONSTANTS IN VIVO  
(3 KG MALE RHESUS MONKEY)

| Compound           | V <sub>max</sub> (mg/min) | K <sub>m</sub> * (mg/liter) | TLV** (mg/liter) |
|--------------------|---------------------------|-----------------------------|------------------|
| Benzene            | 0.3                       | 0.6                         | 0.03             |
| Trichloroethylene  | 0.7                       | 1.0                         | 0.27             |
| Methylene Chloride | 0.7                       | 1.1                         | 0.36             |
| Halothane          | 1.2                       | 7.4                         | 0.40             |

\*Related to Calv

\*\*Threshold limit values recommended by ACGIH in 1979 as TWA.

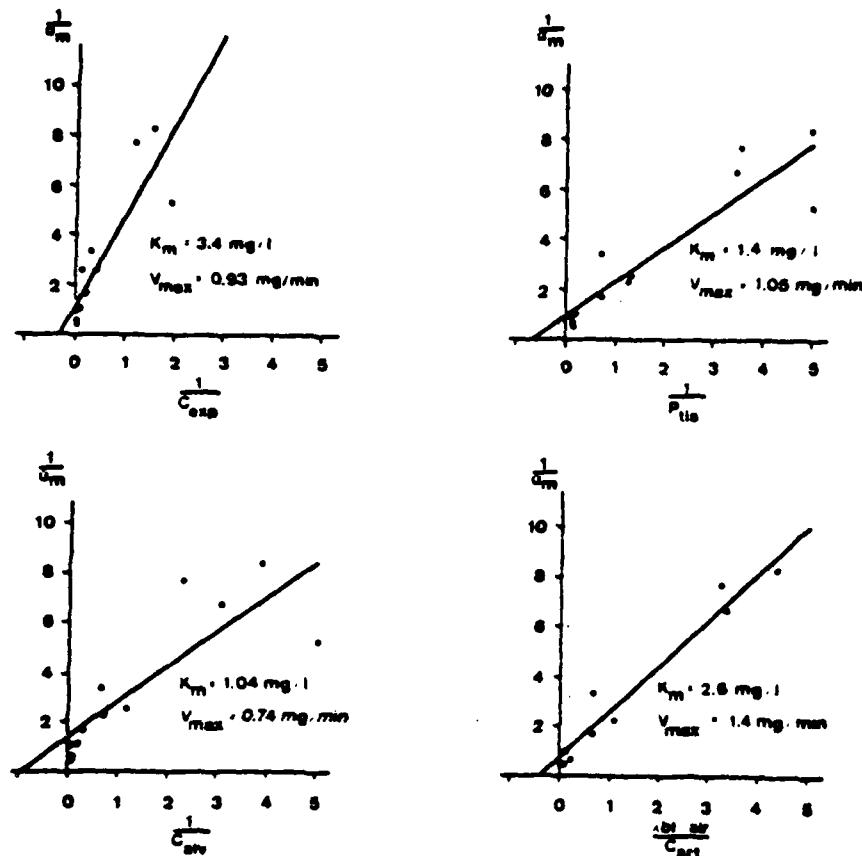


Figure 3. Double reciprocal plot of uptake rates of trichloroethylene versus measured concentrations in inhaled air ( $C_{\text{exp}}$ ), end-exhaled air ( $C_{\text{alv}}$ ), arterial blood ( $C_{\text{art}}$ ), and calculated concentrations in tissues.

$$P_{\text{tis}} = \frac{C_{\text{tis}}}{\lambda_{\text{tis/air}}} = \left( -\frac{\frac{u}{F_{\text{VRG}}}}{C_{\text{art}}} + C_{\text{art}} \right) \frac{1}{\lambda_{\text{bl/air}}}$$

The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

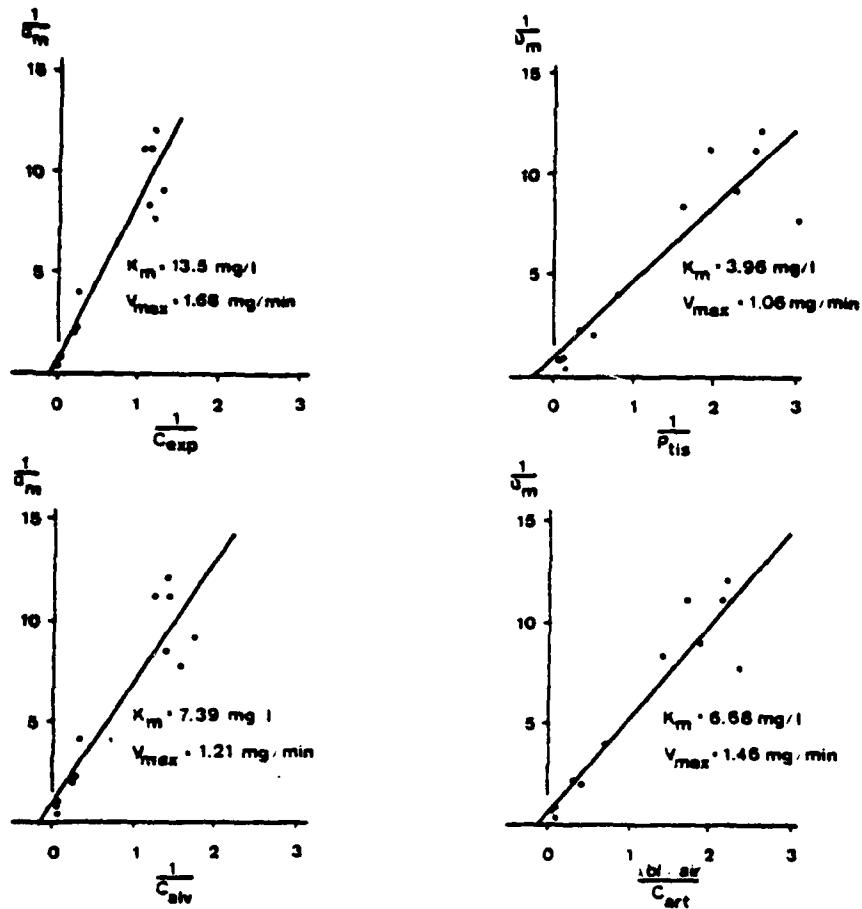


Figure 4. Double reciprocal plot of uptake rates of halothane versus measured concentrations in inhaled air ( $C_{exp}$ ), end-exhaled air ( $C_{alv}$ ), arterial blood ( $C_{art}$ ), and calculated concentrations in tissues.

$$p_{tis} = \frac{C_{tis}}{\lambda_{tis}/air} = \left( -\frac{\dot{u}_m}{F_{VRG}} + C_{art} \right) \frac{1}{\lambda b_l/air}$$

The lines represent optimum fit to experimental data obtained in rhesus monkeys (3 kg males).

The differences in  $K_m$  values might be explained by the three concentration gradients on the pathway of the vapor from the environment to the metabolic site: (1) Vapor concentration entering the lung with each breath is smaller than the exposure concentration because of the dilution by alveolar air from deadspace; (2) When the air reaches the alveoli, the partial pressures in alveolar air and arterial blood are readily equilibrated. Uptake of vapor by arterial blood reduces the concentration further. The concentration decreases, depending on the cardiac output and alveolar ventilation, on the solubility of vapor in blood, and on the concentration of vapor in mixed-venous blood; (3) Arterial blood transfers the vapor to the tissues, where it is retained to the extent that partial pressures in tissue and venous blood are equilibrated. The concentration gradient  $C_{art}/C_{ven}$  in blood which supplies metabolic sites is further increased by metabolic clearance.

At steady state, the partial pressures of nonmetabolized vapor equilibrate, and the vapor concentrations in tissues equal the exposure concentration multiplied by the appropriate partition coefficient. If the vapor is metabolized, the concentrations are reduced.

Employing our nonlinear model (Fiserova-Bergerova et al., in preparation), we examined the conditions under which this method for  $K_m$  and  $V_{max}$  is applicable, and found the following limitations:

(1) Metabolism must be concentration dependent. According to Michaelis-Menten kinetics, this requirement is met if substrate concentrations are smaller than 10  $K_m$ . This means that the studies must be performed in the range of exposure concentrations which are smaller than 10  $K_m$ .

$$C_{exp} < 10 K_m$$

(2) The system cannot be flow-limited. This requires that transportation rate of vapor from environment to the metabolic site is larger than metabolic rate. This condition is met if:

$$\frac{V_{max}}{K_m} < \frac{F \lambda bl/air \dot{V}_{alv}}{\dot{V}_{alv} + F \lambda bl/air}$$

This expression can be rearranged:

$$\frac{V_{max}}{K_m} < F \lambda bl/air \frac{1}{1 + \frac{F}{\dot{V}_{alv}} \lambda bl/air}$$

Optimum conditions for determination are: (a) the vapor is highly susceptible to biotransformation, and (b) the metabolite sites are well perfused or the vapor is well soluble in blood.

We analyzed the tissues of rats and monkeys exposed to different concentrations of halothane and trichloroethylene to determine the effect of exposure concentrations on concentrations of these vapors in tissues. When exposure concentrations were larger than  $K_m$ , the metabolic clearance diminished and the concentration ratios  $C_{exp}/C_{tis}$  increased (Fiserova-Bergerova, unpublished data). The same conclusions were drawn using our nonlinear mathematical model (Fiserova-Bergerova et al., in preparation).

The determination of metabolic rate from pulmonary uptake is also suitable for studying the effect of modifiers on metabolism of inhaled vapors. In experiments similar to those described above, we administered two vapors simultaneously to monkeys. One vapor was administered at a low constant concentration; the concentration of the other vapor - the modifier - was increased in three steps. Data from these experiments are in Figure 5. As the concentration of modifier increased, the pulmonary uptake of the studied vapor decreased. The decrease is probably caused by competitive inhibition of metabolism of the inhaled vapors.

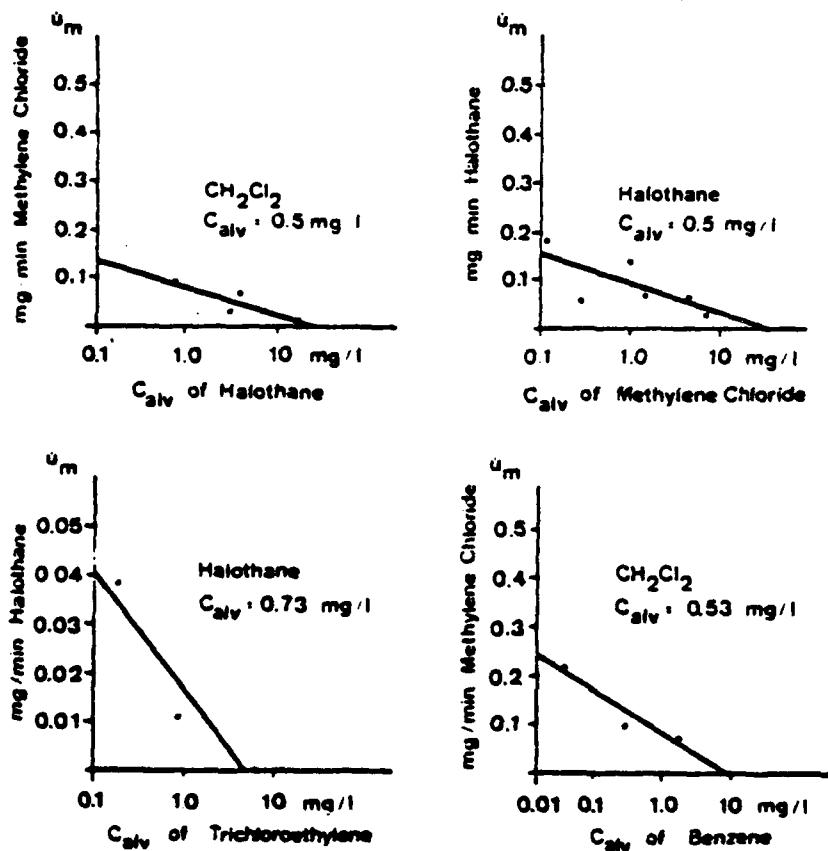


Figure 5. Effect of increasing exposure concentration of vapor-modifier (abscissa) on metabolic rate of the vapor inhaled at constant concentration.

## CONCLUSIONS

We have presented rationales for the determination of metabolic constants *in vivo* from pulmonary uptake rate, and briefly described the procedures and some applications.

The determination of the extent of vapor metabolism from the uptake rate has an advantage over making this determination from excreted metabolites, in that the effect of metabolite distribution and binding in the body, and the effect of renal clearance, are eliminated. Since air sampling is a noninvasive procedure, samples can be collected continuously, or as frequently as needed.

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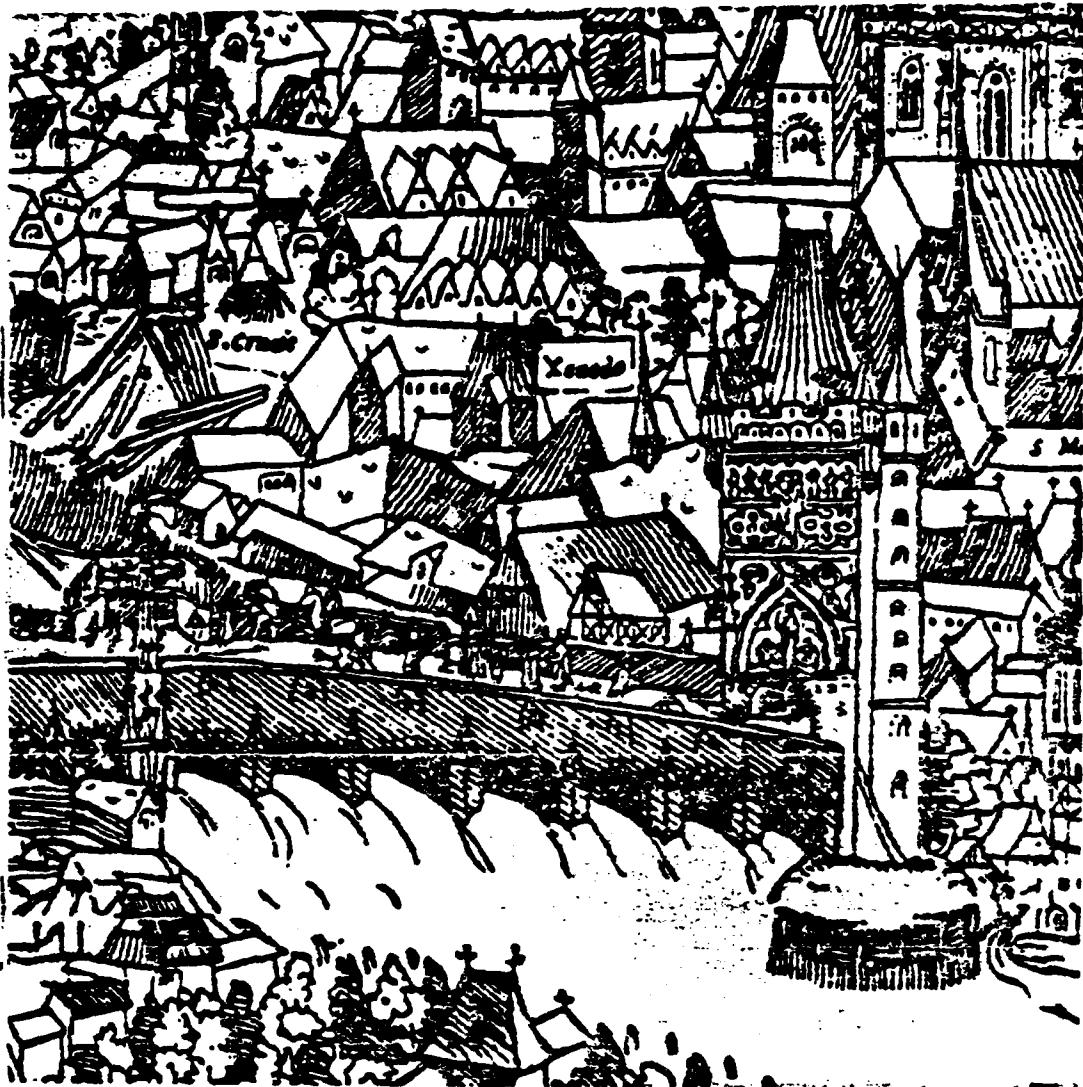
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INTERNATIONAL CONFERENCE ON  
INDUSTRIAL AND ENVIRONMENTAL XENOBIOTICS:  
BIOTRANSFORMATION AND KINETICS

MAY 27 - 30, 1980 PRAGUE - CZECHOSLOVAKIA

# PROGRAMME

PROCEEDINGS

Messrs. SPRINGER-VERLAG accepted publishing.

Vera Fiserova-Bergerova

MODELING OF UPTAKE AND CLEARANCE OF INHALED VAPORS AND GASES

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With progressing technology, toxicologists and hygienists confront the problem of securing safe exposure to an increasing number of air pollutants. The adverse biological effect of pollutants, like the therapeutic effect of drugs, is related to blood concentration and/or time integral of concentration in the target organs. Passage of pollutants from the environment to the target organ has the same significance as migration of drugs from the site of administration to the target organ. Pharmacokinetics describing the transport of drugs in the body is a potent tool for designing dosage regimens of optimum therapeutic effect.<sup>(1)</sup> Methods similar to those used by pharmacokineticists can be employed to design exposures with minimal undesirable biological effects.

Inhalation administration has some specific characteristics: Equilibration of partial pressures of inhaled vapor in the body and in ambient air is the driving force determining uptake.<sup>(2,3)</sup> The equilibration rate depends on pulmonary ventilation, tissue perfusion, and on solubility and clearance of inhaled vapor. The concentration in tissues depends on exposure concentration, exposure duration, and equilibration rate.

Since solubility of inhaled vapor varies for different tissues according to water and lipid content, and since cardiac output is not equally distributed, a multi-compartmental model is needed to describe uptake, distribution, and elimination of inhaled vapors (Figure 1).

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This study was supported by AFOSR 762970 and NIH grant ES01029-02.

In the model, tissues are assigned to the compartment according to perfusion, ability to metabolize the inhaled substance, and solubility of the substance in the tissue.<sup>(4,5)</sup> Lung tissue, functional residual air, and arterial blood form the central compartment 'LG', in which pulmonary uptake and clearance take place. The partial pressure of inhaled vapor equilibrates with four peripheral compartments. Well perfused tissues form two peripheral compartments: BR-compartment includes brain, which lacks capability to metabolize most xenobiotics, and is treated as a separate compartment because of its biological importance and the toxic effect of many vapors and gases on CNS. VRG-compartment includes vessel rich tissues with sites of vapor metabolism such as liver, kidney, glands, heart, and tissues of the gastrointestinal tract. Less perfused tissues are also pooled in two peripheral compartments, according to lipid content: Muscles and skin form compartment 'MG', and adipose tissue and white marrow form compartment 'FG'. It is important to treat the FG-compartment separately, since dumping of lipid soluble vapors in this compartment has a smoothing effect on concentration variation in other tissues, caused by changes in exposure concentration, minute ventilation, and exposure duration. This model is described by a set of five first-order differential equations linear to the first approximation.<sup>(5)</sup>

Mathematical solution of this model is available if the model is pictured as an electric network composed of conductances and capacitances.<sup>(4-9)</sup> In figure 2 'Z' stands for exposure concentration. The values of capacitances 'C' are derived from capacity of tissues to retain the vapor, that is, tissue volumes multiplied by appropriate tissue-air partition coefficients ' $\lambda$ ' at 37°C. The values of conductances  $G_{BR}$ ,  $G_{VRG}$ ,  $G_{MG}$  and  $G_{FG}$  are derived from transportation rates of vapor from the lung to the tissues, that is, blood blow times blood-air partition coefficient (37°C). Alveolar ventilation was substituted for  $G_{LG}$ . ' $G_x$ ' stands for clearance by metabolism. All parameters required by the model can be defined: Physiological parameters can be found in the literature.<sup>(2,3,10-14)</sup> Partition coefficients can be

easily measured. Metabolic clearance can be determined from pulmonary uptake during steady state<sup>(10,15-17)</sup>

The determination of metabolic rate from the uptake rate has an advantage over making this determination from excreted metabolites,<sup>(18)</sup> in that the effect of metabolite distribution and binding in the body, and the effect of renal clearance, are eliminated.

After sufficiently long exposure, the steady state is reached and pulmonary uptake rate equals clearance rate. If clearance does not take place, uptake equals zero and ratios of tissue concentrations to the exposure concentration equal the corresponding partition coefficients. If the vapor is excreted or metabolized during exposure, the ratio of concentrations in alveolar air and in tissue to exposure concentration is smaller than corresponding partition coefficients. The deviation from partition coefficient is directly related to clearance and indirectly related to the flow of vapor to the site of metabolism.

The uptake rate ' $\dot{u}$ ' can be determined from difference of exposure concentration ' $C_{exp}$ ' and vapor concentration in mixed exhaled air ' $C_{exh}$ ', alveolar air ' $C_{alv}$ ' or arterial blood ' $C_{art}$ '.

$$\dot{u} = (C_{exp} - C_{exh}) \dot{V} \quad (1)$$

$$\dot{u} = (C_{exp} - C_{alv}) \dot{V}_{alv} \quad (2)$$

$$\dot{u} = (C_{exp} - \frac{C_{art}}{\lambda_{bl/air}}) \dot{V}_{alv} \quad (3)$$

where ' $\dot{V}$ ' is minute ventilation, ' $\dot{V}_{alv}$ ' is alveolar ventilation ( $\dot{V}_{alv} = 2/3\dot{V}$ ) and ' $\lambda$ ' is partition coefficient.

Determination of uptake rate by analysis of air samples (equations 1 and 2) has the advantage that sampling of mixed exhaled air as well as of end exhaled air (alveolar air) can be done frequently without imposing stress on the subject. However, this method is limited to "cooperative subjects", such as men<sup>(15,19-22)</sup> or animals which tolerate a face mask.<sup>(10,16)</sup> Sampling of arterial blood (equation 3) is more suitable for small experimental animals.<sup>(23)</sup> Anesthesia or any drug administered to subjects undergoing the exposure, might affect the metabolism of inhaled vapor.

For organic solvents, metabolism is the main excretory pathway, and therefore during steady state, metabolic rate  $\dot{u}_m = \dot{u}$ . If flow rate of the vapor to the site of metabolism is much larger than metabolic rate, the measured clearance is intrinsic clearance and

$$G_x = \frac{\dot{u}_m}{C_{exp}} \quad (4)$$

However, for most vapors, pulmonary ventilation and tissue perfusion ('F') affects the metabolic rate, and  $G_x$  must be calculated:

$$\frac{1}{G_x} = \frac{C_{exp}}{\dot{u}} - \frac{1}{V_{alv}} - \frac{1}{F \lambda_{bl/air}} \quad (5)$$

or 
$$\frac{1}{G_x} = \frac{C_{alv}}{\dot{u}} - \frac{1}{F \lambda_{bl/air}} \quad (6)$$

or 
$$\frac{1}{G_x} = \frac{1}{\lambda_{bl/air}} \left( \frac{C_{art}}{\dot{u}} - \frac{1}{F} \right) \quad (7)$$

(4)

$G_x$  can be calculated most accurately if vapor concentration in metabolizing tissue during steady state is known:

$$G_x = \lambda_{tis/air} \frac{\dot{u}_m}{C_{tis}} \quad (8)$$

Perfusion of metabolic rate 'F' can be calculated by subtracting equation 8 from equation 5, 6 or 7 (making  $\dot{u} = \dot{u}_m$ )

$G_x$  is a constant if metabolism follows first order kinetics (low exposure concentration). However, metabolism, like all enzymatic reactions, is a capacity limited process. Therefore  $G_x$  becomes a dependent variable of tissue concentration, and of exposure duration.<sup>(24)</sup>  $G_x$  can be calculated by substituting for ' $\dot{u}_m$ ' in equation 8 from Michaelis-Menten equation:

$$G_x = \frac{\lambda_{tis/air}}{C_{tis}} \cdot \frac{V_{max} C_{tis}}{K_m + C_{tis}} = \frac{V_{max} \lambda_{tis/air}}{K_m + C_{tis}} \quad (9)$$

$K_m$  and  $V_{max}$  can be determined from double reciprocal plot of uptake versus tissue concentration measured during steady state in subjects exposed to different concentrations.

The non-linear element  $G_x$  describing metabolism of limited capacity further complicated the mathematical solution of the model. However, there is a solution for electric network with non-linear element<sup>(25,26)</sup> and computer programs are available.<sup>(4-8,24)</sup> The programs calculate time course of voltages in capacitors and currents in resistors. The voltages 'V' are directly related to tissue concentrations ( $C_{tis} = V \lambda_{tis/air}$ ). Currents are equivalent to uptake rates (or to pulmonary clearance rate) (in  $G_{LG}$ ), metabolic clearance rates (in  $G_x$ ), and retention rates (in  $G_{BR}$ ,  $G_{VRG}$ ,  $G_{MG}$ ,  $G_{FG}$ ). Integrated currents represent amounts retained, metabolized or exhaled.

Examples of the application of modeling to problems of industrial toxicology are in Figures 3 to 7.

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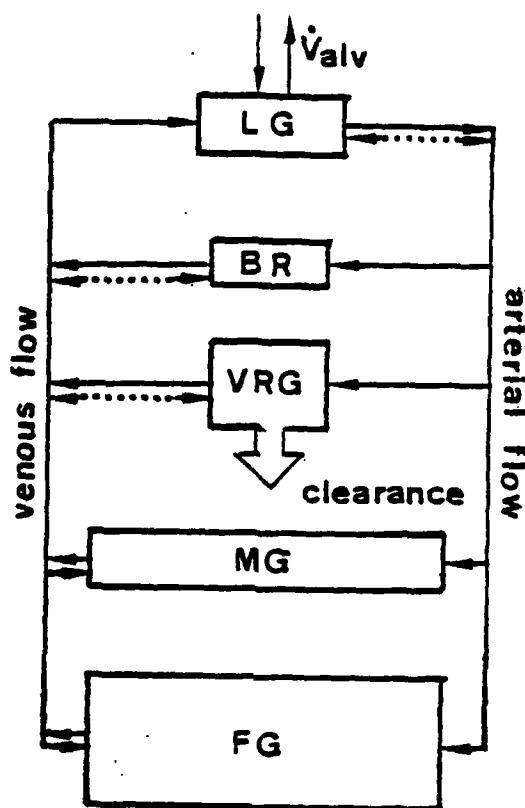
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KEY WORDS:

Clearance - of inhaled vapors  
Concentration excursion  
Compartmental model  
Distribution-of inhaled vapors  
Electric analogue  
Gases - low soluble  
Kinetics  
Metabolism - first order kinetics  
                  capacity limited  
Model - compartmental  
                  mathematical  
                  physiological  
Modeling  
Perfusion  
Solubility  
Vapors - lipid soluble  
Ventilation - alveolar  
                  pulmonary  
Steady state  
Uptake - of inhaled vapors

FIGURE 1

FIVE COMPARTMENTAL MODEL WITH METABOLISM  
IN VESSEL RICH COMPARTMENT



The unbroken arrows indicate blood flow.  
The broken arrows indicate partial pressure equilibration.

FIGURE 2  
FIVE COMPARTMENTAL MODEL PICTURED AS ELECTRIC NETWORK.

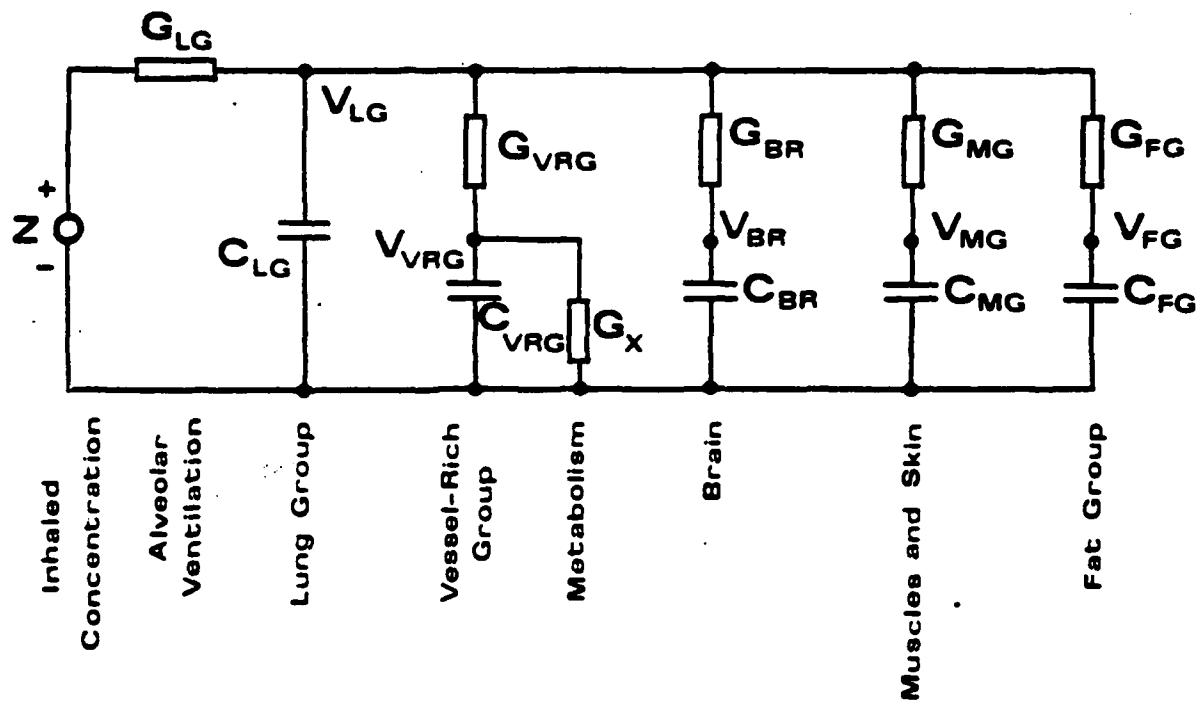
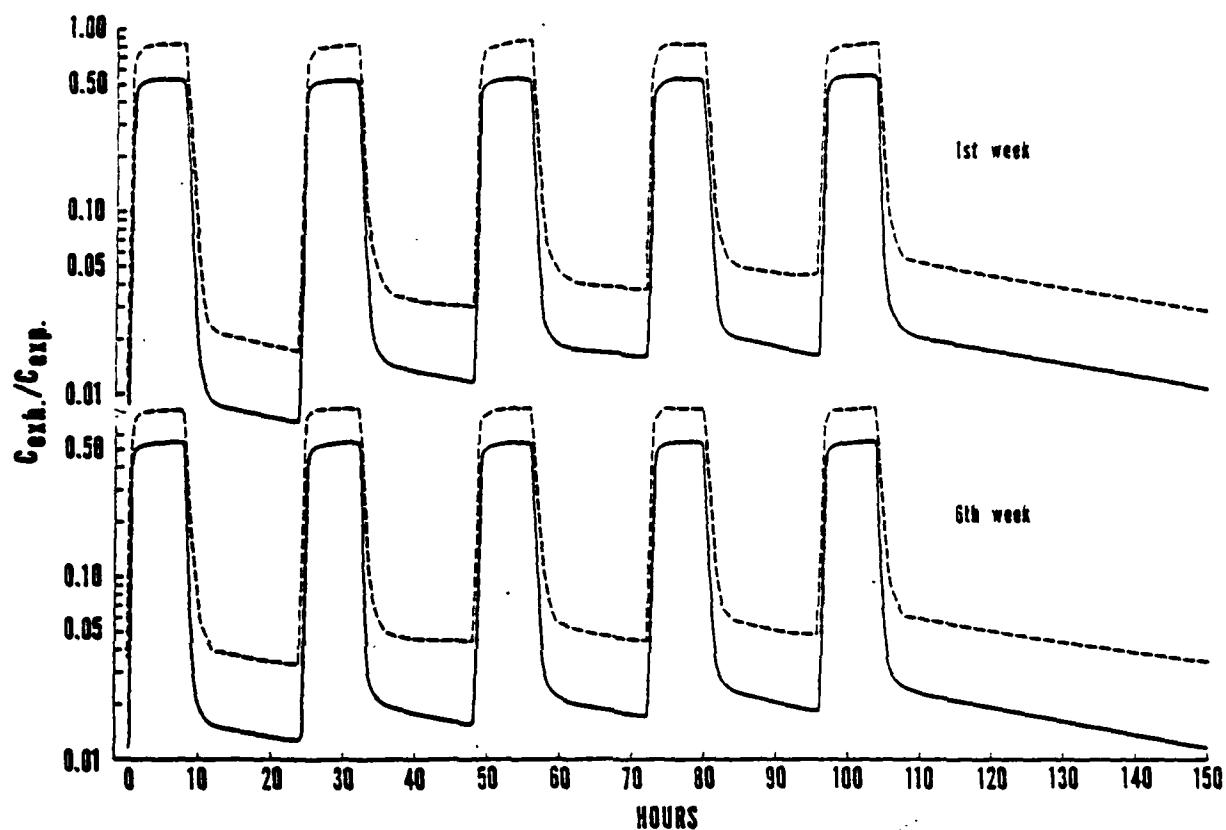


FIGURE 3

PREDICTED CONCENTRATIONS OF BENZENE IN EXHALED AIR ( $C_{EXH}$ ) OF A PERSON EXPOSED TO BENZENE (8 HRS/DAY, 5 DAYS/WEEK) FOR 6 WEEKS



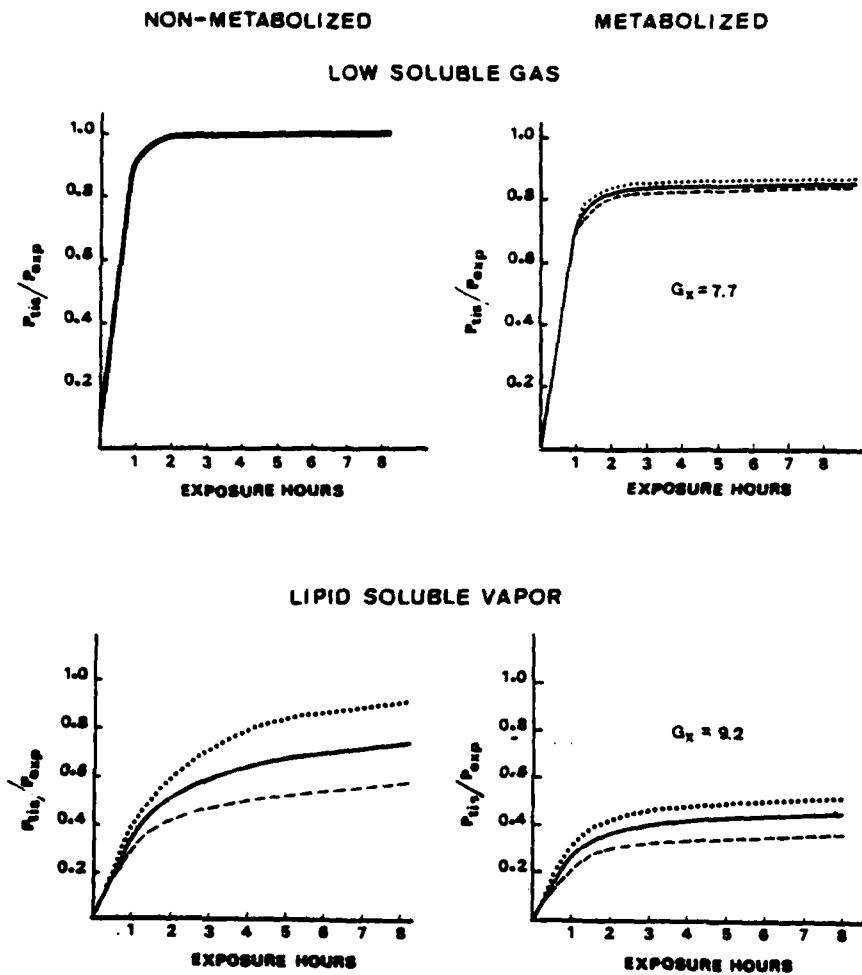
The non-broken line counts with metabolic clearance = 3.6 l/min (15, 27), the broken line represents the hypothetical situation if benzene is not metabolized.

Conclusion: Metabolism reduces benzene concentrations in exhaled air. The concentrations at the end of the week are larger than at the beginning of the week, and for five weeks, rise slightly; on the sixth week, the steady state is reached.

(Reproduced from reference 4)

FIGURE 4

EFFECT OF BODY BUILD ON EQUILIBRATION OF PARTIAL PRESSURES OF INHALED VAPORS IN BRAIN WITH EXPOSURE CONCENTRATION DURING 8-HOUR EXPOSURE



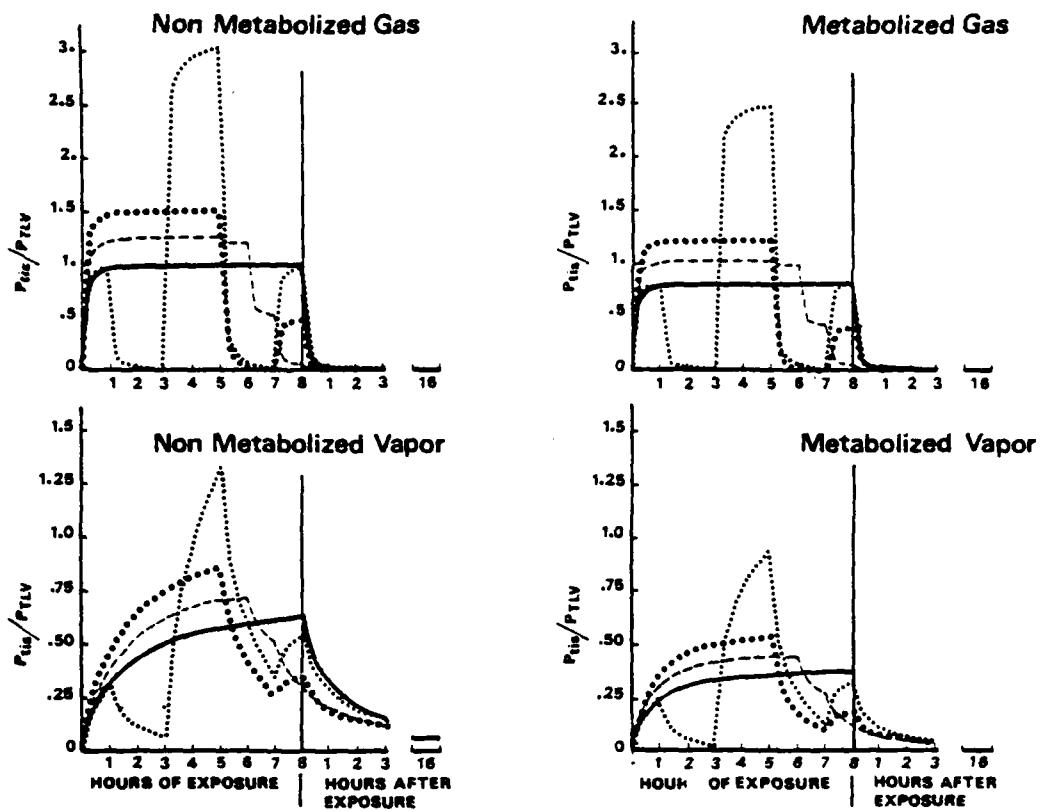
The partial pressure ratios are calculated for brain of a normal build person (solid lines), a slightly obese person (dashed lines) and a slim person (dotted lines). If the lines coincide, the broad solid line is used.

Conclusion: Partial pressure equilibration of low soluble gas in brain is rapid, and body build has no significant effect on brain concentration. Equilibration of lipid soluble vapors is slow, and concentration reached in brain of slim person is much higher than concentration in brain of obese person. If the inhaled vapor is metabolized, the brain concentrations are reduced.

(Reproduced from reference 5)

FIGURE 5

EFFECT OF FLUCTUATION OF EXPOSURE CONCENTRATION ON CONCENTRATION OF  
INHALED VAPORS IN BRAIN



The tissue concentrations are presented as partial pressure ratio of tissue to TLV. Solid lines represent 8-hour exposures to constant concentration (TLV). The interrupted lines represent examples of exposures with excursion factors approved by ACGIH (28): 1.25 (dashed lines), 1.5 (dark dotted lines) and 3 (light dotted lines). Excursions for each hour are as follows:

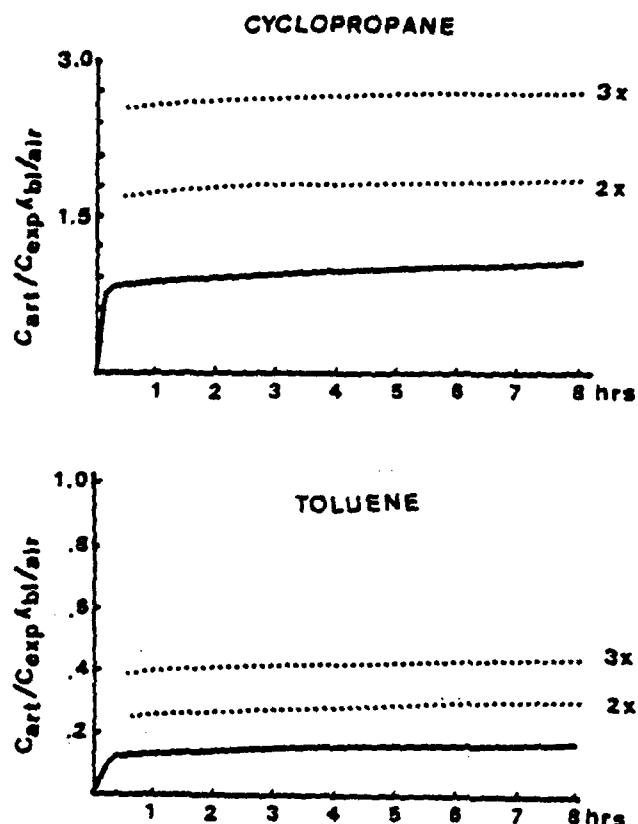
| Excursion Factor | Exposure Hour |      |      |      |      |      |     |       |
|------------------|---------------|------|------|------|------|------|-----|-------|
|                  | 1st           | 2nd  | 3rd  | 4th  | 5th  | 6th  | 7th | 8th   |
| 1.25             | 1.25          | 1.25 | 1.25 | 1.25 | 1.25 | 1.20 | 0.5 | 0.005 |
| 1.5              | 1.5           | 1.5  | 1.5  | 1.5  | 1.5  | 0    | 0   | 0.5   |
| 3.0              | 1.0           | 0    | 0    | 3.0  | 3.0  | 0    | 0   | 1.0   |

Conclusion: Brain concentrations of low soluble gas (upper graphs) fluctuate with exposure concentration. The smoothing effect of FG-compartment on brain concentrations of lipid soluble vapor is apparent in lower graphs. Metabolism diminishes concentrations reached in brain.

(Reproduced from reference 5)

FIGURE 6

EFFECT OF STEL ON CONCENTRATIONS OF CYCLOPROPANE  
AND TOLUENE IN ARTERIAL BLOOD

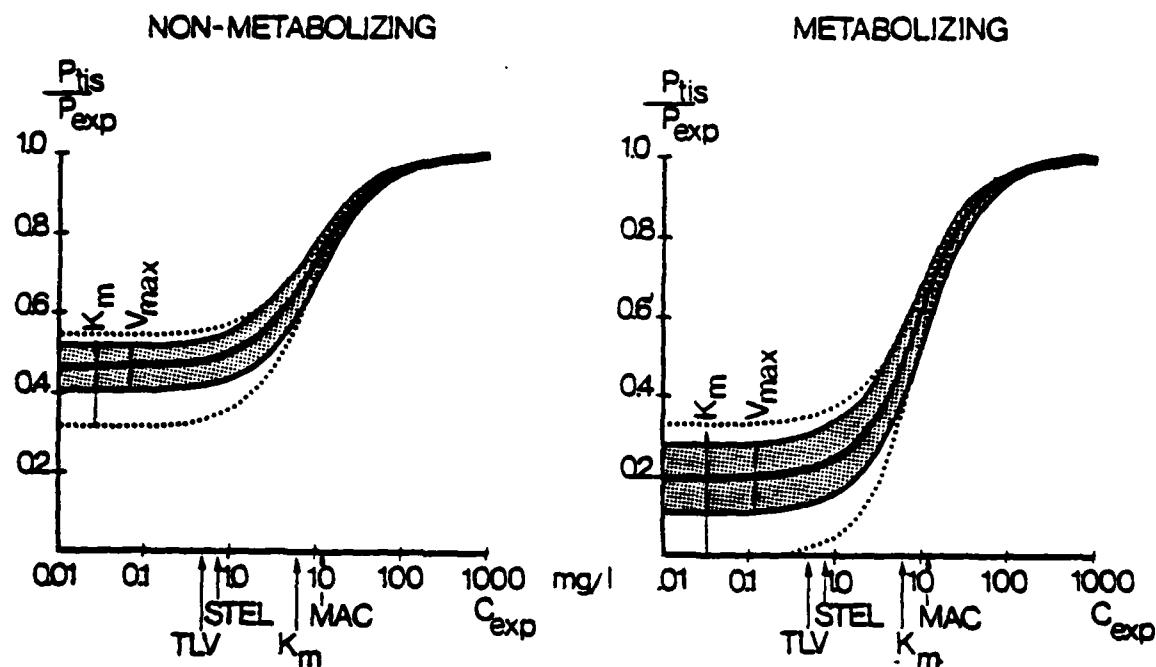


The unbroken lines represent blood concentrations during 8-hour exposure to constant concentrations of cyclopropane or toluene. The broken lines represent blood concentrations at the end of a single 15-minute excursion, with two-fold or three-fold increase of exposure concentration. The values are plotted for single excursions which happen any time during exposure.

Conclusion: The concentration increase in alveolar air (and in tissues) during short excursion is always smaller than the excursion factor (increase in exposure concentration). The increase depends on the excursion duration, excursion factor, duration of exposure prior to excursion, and physical and chemical properties of inhaled compound.

FIGURE /

EFFECT OF CAPACITY LIMITED METABOLISM ON TRICHLOROETHYLENE CONCENTRATIONS  
IN NON-METABOLIZING AND METABOLIZING TISSUES DURING STEADY STATE



For Rhesus Monkey  $K_m = 3.17 \pm 0.73$  mg/l of alveolar air, and  $V_{max} = 1.1 \pm 0.12$  mg/min. (16). The trichloroethylene partial pressure ratios tissue/exposure concentrations are plotted against exposure concentrations. The curves on the left refer to alveolar air, arterial blood, and to tissues in which no metabolism of trichloroethylene occurs. The curves on the right refer to tissues and venous blood, leaving tissues in which trichloroethylene is metabolized. The middle line is calculated for  $K_m = 3.17$  mg/l, and  $V_{max} = 1.1$  mg/min. The shaded area demonstrates the changes caused by variation of  $V_{max}$  in range of 2 S.D. The dotted lines demonstrate the changes caused by variation of  $K_m$  in range of 2 S.D. The arrows indicate the direction of increasing  $V_{max}$  or  $K_m$  respectively. TLV and STEL refer to threshold limit concentrations (28), MAC to minimum anesthetic concentration.

Conclusion: The concentrations in non-metabolizing tissues are larger than in sites of metabolism. At low exposure concentrations, the partial pressures do not equilibrate, and  $C_{tis} < C_{exp} \lambda_{tis/air}$ . When exposure concentration approaches  $K_m$  tissue concentrations start to rise rapidly. At high exposure concentration, the ratio of tissue concentration to exposure concentration approaches the value of corresponding partition coefficient. The tissue concentrations increase with increasing  $K_m$  and decreasing  $V_{max}$ .

